

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068229 A1

(51) International Patent Classification⁷: **A61K 31/44**,
31/47, C07D 213/89, 215/60, 217/08, A61P 35/00, 29/00

(21) International Application Number: PCT/US03/04110

(22) International Filing Date: 11 February 2003 (11.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/354,935 11 February 2002 (11.02.2002) US

(71) Applicant (*for all designated States except US*): **BAYER CORPORATION** [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **DUMAS, Jacques** [FR/US]; 98 Farmview Road, Bethany, CT 06524 (US). **SCOTT, William, J.** [US/US]; 210 Saddle Hill Drive, Guilford, CT 06437 (US). **RIEDL, Bernd** [DE/DE]; Von-der-Golz Strasse 7, 42329 Wuppertal (DE).

(74) Agents: **TRAVERSO, Richard, J.** et al.; Millen, White, Zelano & Branigan, P.C., Arlington Courthouse Plaza 1, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRIDINE, QUINOLINE, AND ISOQUINOLINE N-OXIDES AS KINASE INHIBITORS

(57) Abstract: This invention relates to urea compounds containing a pyridine, quinoline, or isoquinoline functionality which is oxidized at the nitrogen heteroatom and which are useful in the treatment of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated diseases such as inflammation and osteoporosis, and (iii) VEGF mediated diseases such as angiogenesis disorders.



WO 03/068229 A1

PYRIDINE, QUINOLINE, AND ISOQUINOLINE N-OXIDES AS KINASE INHIBITORS

Field of the Invention

5

This invention relates to urea compounds containing a pyridine, quinoline, or isoquinoline functionality, which are useful in the treatment of:

- (i) raf mediated diseases, for example, cancer,
- (ii) p38 mediated diseases such as inflammation and osteoporosis, and
- 10 (iii) VEGF mediated diseases such as angiogenesis disorders.

Background of the Invention

Activation of the Ras signal transduction pathway indicates a cascade of events that
15 have a profound impact on cellular proliferation, differentiation, and transformation. Raf
kinase, a downstream effector of Ras, is a key mediator of these signals from cell surface
receptors to the cell nucleus (Lowy, D. R.; Willumsen, B. M. *Ann. Rev. Biochem.* **1993**,
62, 851; Bos, J. L. *Cancer Res.* **1989**, 49, 4682). It has been shown that inhibiting the
effect of active ras by inhibiting the raf kinase signaling pathway by administration of
20 deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase
or dominant negative MEK, the substrate of raf kinase, leads to the reversion of
transformed cells to the normal growth phenotype (see: Daum et al. *Trends Biochem. Sci.*
1994, 19, 474-80; Fridman et al. *J. Biol. Chem.* **1994**, 269, 30105-8. Kolch et al. (*Nature*
1991, 349, 426-28) have further indicated that inhibition of raf expression by antisense
25 RNA blocks cell proliferation in membrane-associated oncogenes. Similarly, inhibition
of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in
vivo with inhibition of the growth of a variety of human tumor types (Monia et al., *Nat.*
Med. **1996**, 2, 668-75). Thus, small molecule inhibitors of Raf kinase activity are
important agents for the treatment of cancer (Naumann, U.; Eisenmann-Tappe, I.; Rapp,
30 U. R. *Recent Results Cancer Res.* **1997**, 143, 237; Monia, B. P.; Johnston, J. F.; Geiger,
T.; Muller, M.; Fabbro, D. *Nature Medicine* **1996**, 2, 668).

Inhibition of p38 has been shown to inhibit both cytokine production (eg., TNF α , IL-1, IL-6, IL-8) and proteolytic enzyme production (eg., MMP-1, MMP-3) *in vitro* and/or *in vivo*. The mitogen activated protein (MAP) kinase p38 is involved in IL-1 and TNF signaling pathways (Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.;
5 Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heys, J. R.; Landvatter, S. W.; Stricker, J. E.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Yound, P. R. *Nature* 1994, 372, 739).

Clinical studies have linked TNF α production and/or signaling to a number of diseases including rheumatoid arthritis (Maini. *J. Royal Coll. Physicians London* 1996,
10 30, 344). In addition, excessive levels of TNF α have been implicated in a wide variety of inflammatory and/or immunomodulatory diseases, including acute rheumatic fever (Yegin et al. *Lancet* 1997, 349, 170), bone resorption (Pacifci et al. *J. Clin. Endocrinol. Metabol.* 1997, 82, 29), postmenopausal osteoporosis (Pacifci et al. *J. Bone Mineral Res.* 1996, 11, 1043), sepsis (Blackwell et al. *Br. J. Anaesth.* 1996, 77, 110), gram negative
15 sepsis (Debets et al. *Prog. Clin. Biol. Res.* 1989, 308, 463), septic shock (Tracey et al. *Nature* 1987, 330, 662; Girardin et al. *New England J. Med.* 1988, 319, 397), endotoxic shock (Beutler et al. *Science* 1985, 229, 869; Ashkenasi et al. *Proc. Nat'l. Acad. Sci. USA* 1991, 88, 10535), toxic shock syndrome, (Saha et al. *J. Immunol.* 1996, 157, 3869; Lina et al. *FEMS Immunol. Med. Microbiol.* 1996, 13, 81), systemic inflammatory response
20 syndrome (Anon. *Crit. Care Med.* 1992, 20, 864), inflammatory bowel diseases (Stokkers et al. *J. Inflamm.* 1995-6, 47, 97) including Crohn's disease (van Deventer et al. *Aliment. Pharmacol. Therapeu.* 1996, 10 (Suppl. 2), 107; van Dullemen et al. *Gastroenterology* 1995, 109, 129) and ulcerative colitis (Masuda et al. *J. Clin. Lab. Immunol.* 1995, 46, 111), Jarisch-Herxheimer reactions (Fekade et al. *New England J. Med.* 1996, 335, 311), asthma (Amrani et al. *Rev. Malad. Respir.* 1996, 13, 539), adult
25 respiratory distress syndrome (Roten et al. *Am. Rev. Respir. Dis.* 1991, 143, 590; Suter et al. *Am. Rev. Respir. Dis.* 1992, 145, 1016), acute pulmonary fibrotic diseases (Pan et al. *Pathol. Int.* 1996, 46, 91), pulmonary sarcoidosis (Ishioka et al. *Sarcoidosis Vasculitis Diffuse Lung Dis.* 1996, 13, 139), allergic respiratory diseases (Casale et al. *Am. J. Respir. Cell Mol. Biol.* 1996, 15, 35), silicosis (Gossart et al. *J. Immunol.* 1996, 156, 1540; Vanhee et al. *Eur. Respir. J.* 1995, 8, 834), coal worker's pneumoconiosis (Borm

et al. *Am. Rev. Respir. Dis.* 1988, 138, 1589), alveolar injury (Horinouchi et al. *Am. J. Respir. Cell Mol. Biol.* 1996, 14, 1044), hepatic failure (Gantner et al. *J. Pharmacol. Exp. Therap.* 1997, 280, 53), liver disease during acute inflammation (Kim et al. *J. Biol. Chem.* 1997, 272, 1402), severe alcoholic hepatitis (Bird et al. *Ann. Intern. Med.* 1990, 112, 917), malaria (Grau et al. *Immunol. Rev.* 1989, 112, 49; Taverne et al. *Parasitol. Today* 1996, 12, 290) including *Plasmodium falciparum* malaria (Perlmann et al. *Infect. Immun.* 1997, 65, 116) and cerebral malaria (Rudin et al. *Am. J. Pathol.* 1997, 150, 257), non-insulin-dependent diabetes mellitus (NIDDM; Stephens et al. *J. Biol. Chem.* 1997, 272, 971; Ofei et al. *Diabetes* 1996, 45, 881), congestive heart failure (Doyama et al. *Int. J. Cardiol.* 1996, 54, 217; McMurray et al. *Br. Heart J.* 1991, 66, 356), damage following heart disease (Malkiel et al. *Mol. Med. Today* 1996, 2, 336), atherosclerosis (Parums et al. *J. Pathol.* 1996, 179, A46), Alzheimer's disease (Fagarasan et al. *Brain Res.* 1996, 723, 231; Aisen et al. *Gerontology* 1997, 43, 143), acute encephalitis (Ichiyama et al. *J. Neurol.* 1996, 243, 457), brain injury (Cannon et al. *Crit. Care Med.* 1992, 20, 1414; Hansbrough et al. *Surg. Clin. N. Am.* 1987, 67, 69; Marano et al. *Surg. Gynecol. Obstetr.* 1990, 170, 32), multiple sclerosis (M.S.; Coyle. *Adv. Neuroimmunol.* 1996, 6, 143; Matusevicius et al. *J. Neuroimmunol.* 1996, 66, 115) including demyelination and oligodendrocyte loss in multiple sclerosis (Brosnan et al. *Brain Pathol.* 1996, 6, 243), advanced cancer (MucWierzgon et al. *J. Biol. Regulators Homeostatic Agents* 1996, 10, 25), lymphoid malignancies (Levy et al. *Crit. Rev. Immunol.* 1996, 16, 31), pancreatitis (Exley et al. *Gut* 1992, 33, 1126) including systemic complications in acute pancreatitis (McKay et al. *Br. J. Surg.* 1996, 83, 919), impaired wound healing in infection inflammation and cancer (Buck et al. *Am. J. Pathol.* 1996, 149, 195), myelodysplastic syndromes (Raza et al. *Int. J. Hematol.* 1996, 63, 265), systemic lupus erythematosus (Maury et al. *Arthritis Rheum.* 1989, 32, 146), biliary cirrhosis (Miller et al. *Am. J. Gastroenterolog.* 1992, 87, 465), bowel necrosis (Sun et al. *J. Clin. Invest.* 1988, 81, 1328), psoriasis (Christophers. *Austr. J. Dermatol.* 1996, 37, S4), radiation injury (Redlich et al. *J. Immunol.* 1996, 157, 1705), and toxicity following administration of monoclonal antibodies such as OKT3 (Brod et al. *Neurology* 1996, 46, 1633). TNF α levels have also been related to host-versus-graft reactions (Piguet et al. *Immunol. Ser.* 1992, 56, 409) including ischemia reperfusion injury (Colletti et al. *J. Clin. Invest.* 1989,

85, 1333) and allograft rejections including those of the kidney (Maury et al. *J. Exp. Med.* 1987, 166, 1132), liver (Imagawa et al. *Transplantation* 1990, 50, 219), heart (Bolling et al. *Transplantation* 1992, 53, 283), and skin (Stevens et al. *Transplant. Proc.* 1990, 22, 1924), lung allograft rejection (Grossman et al. *Immunol. Allergy Clin. N. Am.* 1989, 9, 153) including chronic lung allograft rejection (obliterative bronchitis; LoCicero et al. *J. Thorac. Cardiovasc. Surg.* 1990, 99, 1059), as well as complications due to total hip replacement (Cirino et al. *Life Sci.* 1996, 59, 86). TNF α has also been linked to infectious diseases (review: Beutler et al. *Crit. Care Med.* 1993, 21, 5423; Degre. *Biotherapy* 1996, 8, 219) including tuberculosis (Rook et al. *Med. Malad. Infect.* 1996, 26, 904), *Helicobacter pylori* infection during peptic ulcer disease (Beales et al. *Gastroenterology* 1997, 112, 136), Chaga's disease resulting from *Trypanosoma cruzi* infection (Chandrasekar et al. *Biochem. Biophys. Res. Commun.* 1996, 223, 365), effects of Shiga-like toxin resulting from *E. coli* infection (Harel et al. *J. Clin. Invest.* 1992, 56, 40), the effects of enterotoxin A resulting from *Staphylococcus* infection (Fischer et al. *J. Immunol.* 1990, 144, 4663), meningococcal infection (Waage et al. *Lancet* 1987, 355; Ossege et al. *J. Neurolog. Sci.* 1996, 144, 1), and infections from *Borrelia burgdorferi* (Brandt et al. *Infect. Immunol.* 1990, 58, 983), *Treponema pallidum* (Chamberlin et al. *Infect. Immunol.* 1989, 57, 2872), cytomegalovirus (CMV; Geist et al. *Am. J. Respir. Cell Mol. Biol.* 1997, 16, 31), influenza virus (Beutler et al. *Clin. Res.* 1986, 34, 491a), Sendai virus (Goldfield et al. *Proc. Nat'l. Acad. Sci. USA* 1989, 87, 1490), Theiler's encephalomyelitis virus (Sierra et al. *Immunology* 1993, 78, 399), and the human immunodeficiency virus (HIV; Poli. *Proc. Nat'l. Acad. Sci. USA* 1990, 87, 782; Vyakarnam et al. *AIDS* 1990, 4, 21; Badley et al. *J. Exp. Med.* 1997, 185, 55).

A number of diseases are thought to be mediated by excess or undesired matrix-destroying metalloprotease (MMP) activity or by an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases (TIMPs). These include osteoarthritis (Woessner et al. *J. Biol. Chem.* 1984, 259, 3633), rheumatoid arthritis (Mullins et al. *Biochim. Biophys. Acta* 1983, 695, 117; Woolley et al. *Arthritis Rheum.* 1977, 20, 1231; Gravallese et al. *Arthritis Rheum.* 1991, 34, 1076), septic arthritis (Williams et al. *Arthritis Rheum.* 1990, 33, 533), tumor metastasis (Reich et al. *Cancer Res.* 1988, 48, 3307; Matrisian et al. *Proc. Nat'l. Acad. Sci., USA* 1986, 83, 9413), periodontal diseases

(Overall et al. *J. Periodontal Res.* 1987, 22, 81), corneal ulceration (Burns et al. *Invest. Ophthalmol. Vis. Sci.* 1989, 30, 1569), proteinuria (Baricos et al. *Biochem. J.* 1988, 254, 609), coronary thrombosis from atherosclerotic plaque rupture (Henney et al. *Proc. Nat'l. Acad. Sci., USA* 1991, 88, 8154), aneurysmal aortic disease (Vine et al. *Clin. Sci.* 1991, 81, 233), birth control (Woessner et al. *Steroids* 1989, 54, 491), dystrophic epidermolysis bullosa (Kronberger et al. *J. Invest. Dermatol.* 1982, 79, 208), degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, temporomandibular joint disease, and demyelinating diseases of the nervous system (Chantry et al. *J. Neurochem.* 1988, 50, 688).

10 Because inhibition of p38 leads to inhibition of TNF α production and MMP production, inhibition of mitogen activated protein (MAP) kinase p38 enzyme provides an approach to the treatment of the above listed diseases including osteoporosis and inflammatory disorders such as rheumatoid arthritis and COPD (Badger, A. M.; Bradbeer, J. N.; Votta, B.; Lee, J. C.; Adams, J. L.; Griswold, D. E. *J. Pharm. Exper. Ther.* 1996, 279, 1453).

15 Vasculogenesis involves the *de novo* formation of blood vessels from endothelial cell precursors or angioblasts. The first vascular structures in the embryo are formed by vasculogenesis. Angiogenesis involves the development of capillaries from existing blood vessels, and is the principle mechanism by which organs, such as the brain and the
20 kidney are vascularized. While vasculogenesis is restricted to embryonic development, angiogenesis can occur in the adult, for example during pregnancy, the female cycle, or wound healing.

25 One major regulator of angiogenesis and vasculogenesis in both embryonic development and some angiogenic-dependent diseases is vascular endothelial growth factor (VEGF; also called vascular permeability factor, VPF). VEGF represents a family of isoforms of mitogens existing in homodimeric forms due to alternative RNA splicing. The VEGF isoforms are highly specific for vascular endothelial cells (for reviews, see: Farrara et al. *Endocr. Rev.* 1992, 13, 18; Neufeld et al. *FASEB J.* 1999, 13, 9).

VEGF expression is induced by hypoxia (Shweiki et al. *Nature* 1992, 359, 843), as well as by a variety of cytokines and growth factors, such as interleukin-1, interleukin-6, epidermal growth factor and transforming growth factor.

To date, VEGF and the VEGF family members have been reported to bind to one or more of three transmembrane receptor tyrosine kinases (Mustonen et al. *J. Cell Biol.*, 1995, 129, 895), VEGF receptor-1 (also known as flt-1 (fms-like tyrosine kinase-1)), VEGFR-2 (also known as kinase insert domain containing receptor (KDR); the murine analogue of KDR is known as fetal liver kinase-1 (flk-1)), and VEGFR-3 (also known as flt-4). KDR and flt-1 have been shown to have different signal transduction properties (Waltenberger et al. *J. Biol. Chem.* 1994, 269, 26988); Park et al. *Oncogene* 1995, 10, 135). Thus, KDR undergoes strong ligand-dependant tyrosine phosphorylation in intact cells, whereas flt-1 displays a weak response. Thus, binding to KDR is a critical requirement for induction of the full spectrum of VEGF-mediated biological responses.

In vivo, VEGF plays a central role in vasculogenesis, and induces angiogenesis and permeabilization of blood vessels. Deregulated VEGF expression contributes to the development of a number of diseases that are characterized by abnormal angiogenesis and/or hyperpermeability processes. Regulation of the VEGF-mediated signal transduction cascade will therefore provide a useful mode for control of abnormal angiogenesis and/or hyperpermeability processes.

Angiogenesis is regarded as an absolute prerequisite for growth of tumors beyond about 1-2 mm. Oxygen and nutrients may be supplied to cells in tumors smaller than this limit through diffusion. However, every tumor is dependent on angiogenesis for continued growth after it has reached a certain size. Tumorigenic cells within hypoxic regions of tumors respond by stimulation of VEGF production, which triggers activation of quiescent endothelial cells to stimulate new blood vessel formation. (Shweiki et al. *Proc. Nat'l. Acad. Sci.*, 1995, 92, 768). In addition, VEGF production in tumor regions where there is no angiogenesis may proceed through the ras signal transduction pathway (Grugel et al. *J. Biol. Chem.*, 1995, 270, 25915; Rak et al. *Cancer Res.* 1995, 55, 4575). In situ hybridization studies have demonstrated VEGF mRNA is strongly upregulated in a wide variety of human tumors, including lung (Mattern et al. *Br. J. Cancer* 1996, 73, 931), thyroid (Viglietto et al. *Oncogene* 1995, 11, 1569), breast (Brown et al. *Human*

Pathol. 1995, 26, 86), gastrointestinal tract (Brown et al. *Cancer Res.* 1993, 53, 4727; Suzuki et al. *Cancer Res.* 1996, 56, 3004), kidney and bladder (Brown et al. *Am. J. Pathol.* 1993, 143I, 1255), ovary (Olson et al. *Cancer Res.* 1994, 54, 1255), and cervical (Guidi et al. *J. Nat'l Cancer Inst.* 1995, 87, 12137) carcinomas, as well as angiosarcoma
5 (Hashimoto et al. *Lab. Invest.* 1995, 73, 859) and several intracranial tumors (Plate et al. *Nature* 1992, 359, 845; Phillips et al. *Int. J. Oncol.* 1993, 2, 913; Berkman et al. *J. Clin. Invest.*, 1993, 91, 153). Neutralizing monoclonal antibodies to KDR have been shown to be efficacious in blocking tumor angiogenesis (Kim et al. *Nature* 1993, 362, 841; Rockwell et al. *Mol. Cell. Differ.* 1995, 3, 315).

10 Overexpression of VEGF, for example under conditions of extreme hypoxia, can lead to intraocular angiogenesis, resulting in hyperproliferation of blood vessels, leading eventually to blindness. Such a cascade of events has been observed for a number of retinopathies, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity (Aiello et al. *New Engl. J. Med.* 1994, 331, 1480; Peer et al. *Lab. Invest.*
15 1995, 72, 638), and age-related macular degeneration (AMD; see, Lopez et al. *Invest. Ophthalmol. Vis. Sci.* 1996, 37, 855).

In rheumatoid arthritis (RA), the in-growth of vascular pannus may be mediated by production of angiogenic factors. Levels of immunoreactive VEGF are high in the synovial fluid of RA patients, while VEGF levels are low in the synovial fluid of patients
20 with other forms of arthritis or with degenerative joint disease (Koch et al. *J. Immunol.* 1994, 152, 4149). The angiogenesis inhibitor AGM-170 has been shown to prevent neovascularization of the joint in the rat collagen arthritis model (Peacock et al. *J. Exper. Med.* 1992, 175, 1135).

Increased VEGF expression has also been shown in psoriatic skin, as well as
25 bullous disorders associated with subepidermal blister formation, such as bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis (Brown et al. *J. Invest. Dermatol.* 1995, 104, 744).

Because inhibition of KDR leads to inhibition of VEGF-mediated angiogenesis and permeabilization, KDR inhibitors will be useful in treatment of diseases
30 characterized by abnormal angiogenesis and/or hyperpermeability processes, including the above listed diseases.

Summary of the Invention

The current invention provides a kinase inhibitor class of novel diarylureas of formula (I) below, pharmaceutical compositions which contain them and methods for their use. The compounds of the present invention are useful as therapeutic compounds for the treatment and prevention of cancer, inflammation, and osteoporosis.

As inhibitors of raf kinase, these compounds are useful in the treatment of tumors and/or cancerous growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid cancers, e.g., murine cancer, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

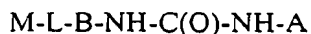
As inhibitors of p38 mediated events, these compounds are useful in treating cytokine mediated disease states and protease mediated disease states in humans or mammals, wherein the cytokine and protease are those whose production is affected by p38. Accordingly, these compounds are useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases as rheumatoid arthritis and osteoporosis.

As inhibitors of VEGF receptor kinases, these compounds are useful in the treatment of diseases where angiogenesis and neovascularization are part of the etiology.

The present invention, therefore, also provides:

- (i) methods for the treatment of raf-mediated disease states in humans or mammals, such as cancer, wherein a compound of formula I is administered, or a salt, prodrug or isolated stereoisomer thereof,
- (ii) methods for the treatment of p38-mediated disease states in humans or mammals, such as inflammation, wherein a compound of formula I is administered, or a salt, prodrug or isolated stereoisomer thereof,
- (iii) methods for the treatment of VEGF-mediated disease states in humans or mammals, such as diabetic retinopathy, wherein a compound of formula I is administered, or a salt, prodrug or isolated stereoisomer thereof.

The invention relates to a compound of formula (I) or a salt, prodrug or isolated stereoisomer thereof (collectively referred to herein as "compounds of this invention"),



I

5

wherein A is selected from the group consisting of

- (i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, COR^1 , COOR^1 , CONR^1R^2 , $\text{NR}^1\text{C(O)R}^2$, halogen, cyano, and nitro;
- 10 (ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, COR^1 , COOR^1 , CONR^1R^2 , $\text{NR}^1\text{C(O)R}^2$, halogen, cyano, and nitro;
- (iii) 5 and 6 membered monocyclic heteroaryl, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3
15 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, COR^1 , COOR^1 , CONR^1R^2 , NR^1COR^2 , halogen, cyano, and nitro; and
- (iv) 8-10 membered bicyclic heteroaryl, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents
20 independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, COR^1 , COOR^1 , CONR^1R^2 , NR^1COR^2 , halogen, cyano, and nitro.

B is selected from the group consisting of

- (i) phenylene, optionally substituted with 1-3 substituents independently selected from the group consisting of $\text{C}_1\text{-C}_5$ linear or branched alkyl, $\text{C}_1\text{-C}_5$ linear or branched
25 haloalkyl, $\text{C}_1\text{-C}_3$ alkoxy, hydroxy, amino, $\text{C}_1\text{-C}_3$ alkylamino, $\text{C}_1\text{-C}_3$ dialkylamino, halogen, cyano, and nitro;
- (ii) naphthylene, optionally substituted with 1-3 substituents independently selected from the group consisting of $\text{C}_1\text{-C}_5$ linear or branched alkyl, $\text{C}_1\text{-C}_5$ linear or branched haloalkyl, $\text{C}_1\text{-C}_3$ alkoxy, hydroxy, amino, $\text{C}_1\text{-C}_3$ alkylamino, $\text{C}_1\text{-C}_3$ dialkylamino,
30 halogen, cyano, and nitro;

- (iii) 5 and 6 membered monocyclic heteroaryl-ene, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched haloalkyl, C₁-C₃ alkoxy, hydroxy, amino, C₁-C₃ alkylamino, C₁-C₃ dialkylamino, halogen, cyano, and nitro; and
- (iv) 8-10 membered bicyclic heteroaryl-ene, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched haloalkyl, C₁-C₃ alkoxy, hydroxy, amino, C₁-C₃ alkylamino, C₁-C₃ dialkylamino, halogen, cyano, and nitro.

L is selected from the group consisting of :

- (a) $-(CH_2)_m-O-(CH_2)_l-$,
 (b) $-(CH_2)_m-(CH_2)_l-$,
 (c) $-(CH_2)_m-C(O)-(CH_2)_l-$,
 15 (d) $-(CH_2)_m-NR^{3a}-(CH_2)_l-$,
 (e) $-(CH_2)_m-NR^{3a}C(O)-(CH_2)_l-$,
 (f) $-(CH_2)_m-S-(CH_2)_l-$,
 (g) $-(CH_2)_m-C(O)NR^{3a}-(CH_2)_l-$,
 (h) $-(CH_2)_m-CF_2-(CH_2)_l-$,
 20 (i) $-(CH_2)_m-CCl_2-(CH_2)_l-$,
 (j) $-(CH_2)_m-CHF-(CH_2)_l-$, and
 (k) $-(CH_2)_m-CR^{3a}(OH)-(CH_2)_l-$;
 (l) $-(CH_2)_m-C\equiv C-(CH_2)_l-$;
 (m) $-(CH_2)_m-C=C-(CH_2)_l-$;
 25 (n) a single bond; and
 (o) $-(CH_2)_m-CR^{3a}R^{3b}-(CH_2)_l-$;

wherein m and l are integers independently selected from 0-4.

M is selected from the group consisting of

a) pyridine-1-oxide substituted 1 to 3 times by a substituent selected from the group consisting of $-C(O)NR^4R^5$, $-C(NR^4)R^5$, $-C(O)R^4$, $-SO_2R^4$, and $-SO_2NR^4R^5$, which is optionally additionally substituted by Z_r ;

b) quinoline-1-oxide, which is optionally substituted by Z_n ; and

5 c) isoquinoline-1-oxide, which is optionally substituted by Z_n ;

wherein

r is 0-2,

n is 0-3, and

10 each Z is independently selected from the group consisting of R^4 , halogen, cyano, $-CO_2R^4$, $-C(O)R^4$, $-C(O)NR^4R^5$, $-NO_2$, $-OR^4$, $-NR^4R^5$, $-NR^4C(O)OR^5$, $-NR^4C(O)R^5$, $-S(O)_pR^4$, and $-SO_2NR^4R^5$.

Each R^1 , R^2 , R^4 and R^5 are independently selected from the group consisting of:

15 (a) hydrogen,

(b) C_1 - C_5 linear, branched, or cyclic alkyl,

(c) phenyl,

(d) 5-6 membered monocyclic heteroaryl heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6

20 heteroatoms selected from the group consisting of O, N and S,

(e) C_1 - C_3 alkyl-phenyl,

(f) C_1 - C_3 alkyl heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, said heteroaryl including 5-6 membered monocyclic and 8-10 membered bicyclic heteroaryl, and

25 (g) up to per-halo substituted C_1 - C_5 linear or branched alkyl.

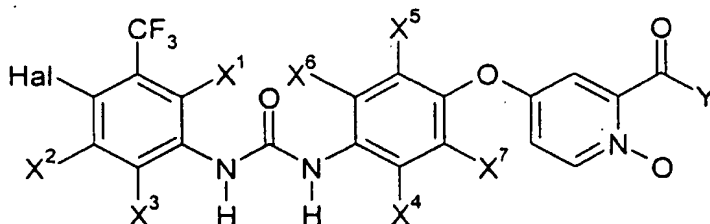
R^{3a} and R^{3b} are independently, hydrogen or C_1 - C_5 linear or branched alkyl.

30 Each R^1 , R^2 , R^4 and R^5 , when not hydrogen or perhalo substituted C_1 - C_5 linear or branched alkyl, are optionally substituted with 1-3 substituents independently selected from the group consisting of C_1 - C_5 linear or branched alkyl, up to perhalo substituted C_1 -

C₅ linear or branched alkyl, C₁-C₃ alkoxy, hydroxy, amino, C₁-C₃ alkylamino, C₁-C₆ dialkylamino, halogen, cyano, and nitro;

and p and q are integers each independently selected from 0, 1, or 2.

5 The compounds of this invention do not include compounds of Formula II below, or salts, prodrugs or isolated stereoisomers thereof,



II

wherein,

Y is OR¹ or NHR²,

15 Hal is chlorine or bromine,

R¹ is H or C₁-C₆ alkyl

R² is H, OH, CH₃ or CH₂OH,

X¹ to X⁷ are each, independently, H, OH or O(CO)C₁-C₄ alkyl.

20 For compounds of formula II, the C(O)Y substituted pyridine-1-oxide conforms to M of formula I, the X⁴ to X⁷ substituted phenyl conforms to B of formula I, the oxygen bridge, -O-, conforms to L of formula I and the X¹ to X³ substituted 3-trifluoromethyl-4-halo-phenyl conforms to A of formula I.

25 It is understood that the term "pyridine-1-oxide" used throughout this document includes those structures referred to in the art as 1-oxo-pyridine and 1-hydroxy-pyridine. For example, ChemInnovation Software, Inc. NomenclatorTM v. 3.01 identifies

compounds of formula II where $Y = \text{NHCH}_3$, $\text{Hal} = \text{Cl}$ and $X^1 - X^7 = \text{H}$, drawn in ChemDraw, as N-[4-chloro-3-(trifluoromethyl)phenyl]({4-[1-hydroxy-2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl}amino)carboxamide. The same remark applies to the quinoline-1-oxides and the isoquinoline-1-oxides.

5

Suitable substituted and unsubstituted heteroaryl groups for the compounds of this invention, such as those for A and B of formula I, include, but are not limited to monocyclic heteroaryl groups such as 2- or 3-furyl, 2- or 3-thienyl, 2- or 4-triazinyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,3,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl and 2-,3-pyrazinyl.

15

Suitable substituted and unsubstituted heteroaryl groups for the compounds of this invention, such as those for A and B of formula I, include, but are not limited to bicyclic heteroaryl groups. Examples of bicyclic heteroaryl rings include 5-5, 5-6, and 6-6 fused bicycles, where one of the rings is one of the above heteroaryl rings and the second ring is either benzene or another heteroaryl ring, for example 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-indazolyl (benzopyrazolyl), 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5- 6- or 7-benzisoxazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benz-1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, 8- isoquinolinyl, or 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl.

25

More specifically, the substituted heteroaryl groups can be, for example, 5-methyl-2-thienyl, 4-methyl-2-thienyl, 1-methyl-3-pyrryl, 1-methyl-3-pyrazolyl, 5-methyl-2-thiazolyl, 5-methyl-1,2,4-thiadiazol-2-yl and others.

30

Suitable linear alkyl groups and alkyl portions of groups, e.g., alkoxy, alkylphenyl and alkylheteroaryl etc. throughout include methyl, ethyl, propyl, butyl, pentyl, etc.

Suitable branched alkyl groups include all branched isomers such as isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, etc.

The term "up to perhalo substituted linear and branched alkyl," includes alkyl groups having one alkyl hydrogen replaced with halogen, alkyl groups wherein all
5 hydrogens are replaced with halogen, alkyl groups wherein more than one but less than all hydrogens are replaced by halogen and alkyl groups having alkyl hydrogens replaced by halogen and other substituents.

Suitable halogen groups include F, Cl, Br, and/or I, from one to per-substitution
10 (i.e. all H atoms on a group replaced by a halogen atom) being possible where an alkyl group is substituted by halogen, mixed substitution of halogen atom types also being possible on a given moiety. Preferred halogens are Cl, Br and F.

The term "cycloalkyl", as used herein, refers to cyclic structures having 3-8
15 members in the ring such as cyclopropyl, cyclobutyl and cyclopentyl and cyclic structures having 3-8 members with alkyl substituents such that, for example, "C₃ cycloalkyl" includes methyl substituted cyclopropyl groups.

The term "saturated carbocyclic moieties" defines only the cyclic structure, i.e.
20 cyclopentyl, cyclohexyl, etc. Any alkyl substitution on these cyclic structures is specifically identified.

Particularly preferred compounds of this invention are defined by formula I, wherein:
25 A is selected from phenyl, naphthyl, furyl, isoindolyl, oxadiazolyl, oxazolyl, isooxazolyl, indolyl, indazolyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiadiazolyl, thiazolyl and thienyl,
B is selected from phenylene, naphthylene, thienylene, furylene, pyridine-ene, quinoline-
30 ene, isoquinoline-ene, indole-ene,

L is selected from -CH₂O-, -OCH₂-, -O-, a single bond, -CH₂-, -NH-, -N(CH₃)-, -N(CH₃)CH₂-, -NC₂H₄-, -C(O)-, -NHCH₂-, -N(CH₃)C(O)-, -NHC(O)-, -CH₂N(CH₃)-, -C(O)NH-, -CH₂S-, -SCH₂-, -S-, -C(O)NCH₃-, -CH₂C(O)N(CH₃)-, -C(O)N(CH₃)CH₂-, -CF₂-, -CCl₂-, -CHF- and -CH(OH)-, and

5 M is defined as above.

Particularly preferred substituents for B include methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, *tert*-butyl, *sec*-butyl, methylethyl, methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br and F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino, Preferred substituents for A include methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, i-propyl, t-butyl, methylethyl, methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, methyl sulfonyl, ethoxy, propoxy, butyoxo, pentoxy, phenoxy, pyridyloxy, Cl, Br, F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino. Preferred substituents for A further include substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, isoindolyl, pyrazolyl, pyridazinyl, pyrrolyl, imidazolyl, indazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, benzothiazolyl, benzyl, and pyridylmethyl.

Preferred substituents for A also include:

20 NH(C₁-C₅ alkyl, phenyl or pyridinyl), such as aminophenyl;
 N(C₁-C₅ alkyl)(C₁-C₅ alkyl, phenyl or pyridinyl), such as diethylamino and dimethyl amino;
 S(O)₂ (C₁-C₅ alkyl); such as methylsulfonyl;
 SO₂NH(C₁-C₅ alkyl);
 25 SO₂N(C₁-C₅ alkyl)(C₁-C₅ alkyl);
 NHSO₂(C₁-C₅ alkyl);
 N(C₁-C₃ alkyl) SO₂(C₁-C₅ alkyl);
 CO(C₁-C₆ alkyl, phenyl or pyridinyl);
 COO(C₁-C₆ alkyl, phenyl or pyridinyl), such as C(O)OCH₃, -C(O)OCH₂CH₃, -
 30 C(O)OCH₂CH₂CH₃;
 COOH;

CONH₂ (carbamoyl);

CONH(C₁-C₆ alkyl, phenyl or pyridinyl), such as N-methylethyl carbamoyl, N-methyl carbamoyl, N-ethylcarbamoyl, N-dimethylamino ethyl carbamoyl;

5 CON(C₁-C₆ alkyl, phenyl or pyridinyl)(C₁-C₆ alkyl, phenyl or pyridinyl), such as N-dimethyl carbamoyl;

NHCO(C₁-C₅ alkyl, phenyl or pyridinyl) and

N(C₁-C₅ alkyl)CO(C₁-C₅ alkyl); each of the above substituents are optionally partially or fully halogenated, such as difluoromethyl sulfonyl and trifluoromethyl sulfonyl.

10

An embodiment of this invention includes compounds of this invention wherein in formula I, A, and B are one of the following combinations and M is as defined above:

A= phenyl, B=phenylene,

A= phenyl, B=pyridinyl-ene,

15 A=phenyl, B = naphthylene,

A= phenyl, B= quinolinyl-ene,

A= phenyl, B= isoquinolinyl-ene,

A= pyridinyl, B=phenylene,

A= pyridinyl, B=pyridinyl-ene,

20 A= pyridinyl, B = naphthylene,

A= pyridinyl, B= quinolinyl-ene,

A= pyridinyl, B= isoquinolinyl-ene,

A= naphthyl , B=phenylene,

A= naphthyl , B=pyridinyl-ene,

25 A= naphthyl , B = naphthylene,

A= naphthyl , B= quinolinyl-ene,

A= naphthyl , B= isoquinolinyl-ene,

A= isoquinolinyl, B=phenylene,

A= isoquinolinyl, B=pyridinyl-ene,

30 A= isoquinolinyl, B = naphthylene,

A= isoquinolinyl, B= quinolinyl-ene

- A= isoquinolinyl, B= isoquinolinyl-ene,
A=quinolinyl, B=phenylene,
A= quinolinyl, B=pyridinyl-ene,
A= quinolinyl, B = naphthylene,
5 A= quinolinyl, B= quinolinyl-ene
A= quinolinyl, B= isoquinolinyl-ene,
A=pyrazolyl, B=phenylene,
A= pyrazolyl, B=pyridinyl-ene,
A= pyrazolyl, B = naphthylene,
10 A= pyrazolyl, B= quinolinyl-ene,
A= pyrazolyl, B= isoquinolinyl-ene,
A=isoxazolyl, B=phenylene,
A= isoxazolyl, B=pyridinyl-ene,
A= isoxazolyl, B = naphthylene,
15 A= isoxazolyl, B= quinolinyl-ene,
A= isoxazolyl, B= isoquinolinyl-ene.
A=indazolyl, B=phenylene,
A= indazolyl, B=pyridinyl-ene,
A= indazolyl, B = naphthylene,
20 A= indazolyl, B= quinolinyl-ene and
A= indazolyl, B= isoquinolinyl-ene.

The invention further relates to processes and methods of preparing the novel compounds
25 of this invention.

The invention further relates to pharmaceutical compositions comprising one or
more compounds of this invention, or a purified stereoisomer, a pharmaceutically
acceptable salt, or a prodrug of a compound of formula (I). The invention also relates to
30 compounds *per se*, of formula I.

One of ordinary skill in the art will recognize that some of the compounds of Formula (I) can exist in different geometrical isomeric forms. A number of the compounds of Formula I possess asymmetric carbons and can therefore exist in racemic and optically active forms as well as in the form of racemic or nonracemic mixtures thereof, and in the form of diastereomers and diastereomeric mixtures. All of these compounds, including *cis* isomers, *trans* isomers, diastereomeric mixtures, racemates, nonracemic mixtures of enantiomers, substantially pure, and pure enantiomers, are considered to be within the scope of the present invention and are collectively referred to when reference is made to compounds of this invention.

10

Methods of separation of enantiomeric and diastereomeric mixtures are well known to one skilled in the art. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. The optically active bases or acids are liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of a chiral chromatography column (e.g., chiral HPLC columns) optimally chosen to maximize the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel OJ. The optically active compounds of Formula (I) can likewise be obtained by utilizing optically active starting materials. The present invention encompasses any isolated racemic or optically active form of compounds described in Formula I which possess raf, p38, and/or VEGFR inhibitory activity. The term stereoisomer is understood to encompass diastereoisomers, enantiomers, geometric isomers, etc. Herein, substantially pure enantiomers is intended to mean that no more than 5% w/w of the corresponding opposite enantiomer is present.

30

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Salts of this invention are especially the pharmaceutically acceptable salts of compounds of formula (I) such as, for example, organic or inorganic acid addition salts of compounds of formula (I). Suitable inorganic acids include but are not limited to halogen acids (such as hydrochloric acid and hydrobromic acid), sulfuric acid, or phosphoric acid. Suitable organic acids include but are not limited to carboxylic, phosphonic, sulfonic, or sulfamic acids, with examples including acetic acid, propionic acid, octanoic acid, decanoic acid, trifluoroacetic acid, dodecanoic acid, glycolic acid, lactic acid, 2- or 3-hydroxybutyric acid, γ -aminobutyric acid (GABA), gluconic acid, glucosemonocarboxylic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azeiaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids (such as glutamic acid, aspartic acid, N-methylglycine, acetylaminoacetic acid, N-acetylasparagine or N-acetylcysteine), pyruvic acid, acetoacetic acid, methanesulfonic acid, tri-fluoromethane sulfonic acid, 4-toluene sulfonic acid, benzenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, phosphoserine, and 2- or 3-glycerophosphoric acid.

20

In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ , Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption,

30

biostability and release time (see *"Pharmaceutical Dosage Form and Drug Delivery Systems"* (Sixth Edition), edited by Ansel et al., published by Williams & Wilkins, pages 27-29, (1995) which is hereby incorporated by reference). Commonly used prodrugs of the disclosed oxazolyl-phenyl-2,4-diamino-pyrimidine compounds are designed to take
5 advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics*
10 (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 11-13, (1996), which is hereby incorporated by reference).

The invention also relates to methods for treating and preventing diseases, for example, hyper-proliferative, inflammatory and angiogenesis disorder and osteoporosis in
15 mammals by administering a compound of this invention or a pharmaceutical composition comprising one or more compounds of this invention.

An embodiment of the present invention is a method for treating diseases in humans and/or other mammals which are mediated by the VEGF induced signal transduction pathway which comprises administering a compound of this invention to a
20 human or other mammal.

Another embodiment of this invention is a method for treating diseases in humans and/or other mammals which are characterized by abnormal angiogenesis or hyperpermeability processes with a compound of this invention to a human or other
25 mammal.

A compound according to the invention can be administered simultaneously with another angiogenesis inhibiting agent to a patient with such a disorder, in the same formulation or, more typically in separate formulations and, often, using different
30 administration routes. Administration can also be sequentially, in any order.

A compound according to the invention can be administered in tandem with another angiogenesis inhibiting agent, wherein a compound according to the invention can be administered to a patient once or more per day for up to 28 consecutive days with the concurrent or intermittent administration of another angiogenesis inhibiting agent
5 over the same total time period

The invention also relates to a method of treating or preventing cancer and other hyperproliferative disorders by administering a compound of this invention or a pharmaceutical composition comprising one or more compounds of this invention,
10 optionally in combination with a cytotoxic agent.

Optional anti-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the Merck Index, (1996), which is hereby incorporated by reference, such
15 as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycin), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone,
20 procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Additional cytotoxic agents include oxaliplatin, gemcitabine, gefinitib, taxotere, ara A, ara C, herceptin, BCNU, CCNU, DTIC, and actinomycin D. Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which
30 is hereby incorporated by reference such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-

difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, 5 pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone, 10 irinotecan, raloxifen and topotecan.

The invention also relates to a pharmaceutical preparation which comprises (1) quantities of (a) a compound according to the invention (b) at least one other cytotoxic or cytostatic agent in amounts which are jointly effective for treating a cancer, where any 15 component (a) or (b) can also be present in the form of a pharmaceutically acceptable salt if at least one salt-forming group is present, with (2) one or more pharmaceutically acceptable carrier molecules.

The present invention provides methods for treating a cancer in a mammal, 20 especially a human patient, comprising administering an a compound according to the invention optionally in combination with a cytotoxic or cytostatic chemotherapeutic agent including, but not limited to, DNA topoisomerase I and II inhibitors, DNA intercalators, alkylating agents, microtubule disruptors, hormone and growth factor receptor agonists or antagonists, other kinase inhibitors and antimetabolites. The methods of the present 25 invention can be used to treat a variety of mammal hyperproliferative disorders as defined in this specification. The compound according to the invention and the cytotoxic or cytostatic agent are administered to a mammal in quantities which together are therapeutically effective against proliferative diseases. Thus, the compound according to the invention is effective for raf kinase-mediated cancers. However, these compounds are 30 also effective for cancers not mediated by raf kinase.

A compound according to the invention can be administered simultaneously with a cytotoxic or cytostatic agent to a patient with a cancer, in the same formulation or, more typically in separate formulations and, often, using different administration routes. Administration can also be sequentially, in any order.

5

A compound according to the invention can be administered in tandem with the cytotoxic or cytostatic agent, wherein a compound according to the invention can be administered to a patient once or more per day for up to 28 consecutive days with the concurrent or intermittent administration of a cytotoxic or cytostatic agent over the same total time period.

10

A compound according to the invention can be administered to a patient at an oral, intravenous, intramuscular, subcutaneous, or parenteral dosage which can range from about 0.1 to about 200 mg/kg of total body weight and the cytotoxic or cytostatic agent can be administered to a patient at an intravenous, intramuscular, subcutaneous, or parenteral dosage which can range from about 0.1 mg to 200 mg/kg of patient body weight.

15

This invention further relates to kits comprising separate doses of the two mentioned chemotherapeutic agents in separate containers. The combinations of the invention can also be formed in vivo, e.g., in a patient's body.

20

The term "cytotoxic" refers to an agent which can be administered to kill or eliminate a cancer cell. The term "cytostatic" refers to an agent which can be administered to restrain tumor proliferation rather than induce a cytoreduction yielding the elimination of the cancer cell from the total viable cell population of the patient. The chemotherapeutic agents described herein, e.g., irinotecan, vinorelbine, gemcitabine, and paclitaxel are considered cytotoxic agents. These cytotoxic and cytostatic agents have gained wide spread use as chemotherapeutics in the treatment of various cancer types and are well known in the art. These and other cytotoxic/cytostatic agents can be

25

30

administered in the conventional formulations and regimens in which they are known for use alone.

Description of Treatment of Hyperproliferative Disorders

5 Cancer and hyperproliferative disorders are defined as follows. These disorders include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

10

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

15

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

20

Examples of brain cancers include, but are not limited to brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

25

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer.

Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

5 Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

10

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

15 Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer. Lymphomas
20 include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma,
25 malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma. Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in man, but also exist with a similar
30 etiology in other mammals, and can be treated by pharmaceutical compositions of the present invention.

Conditions within a human or other mammal which can be treated by administering a compound of this invention include tumor growth, retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity and age
5 related macular degeneration; psoriasis, or bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis, rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurismal aortic, birth control, dystrophic epidermolysis
10 bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, temporomandibular joint disease or demyelinating disease of the nervous system.

Methods of interest treat combinations of conditions such as rheumatic fever,
15 bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's
20 pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligodendrocyte loss in multiple
25 sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft
30 rejection (obliterative bronchitis) or complications due to total hip replacement.

Also provided is a method for treating an infectious disease selected from the group consisting of tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

General Preparative Methods

The compounds of the invention may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are presented to aid the reader in synthesizing the compounds of the present invention, with more detailed particular examples being presented below in the experimental section describing the working examples.

All variable groups of these methods are as described in the generic description if they are not specifically defined below. When a variable group or substituent with a given symbol is used more than once in a given structure, it is to be understood that each of these groups or substituents may be independently varied within the range of definitions for that symbol. It is recognized that compounds of the invention with each claimed optional functional group cannot be prepared with each of the below-listed methods. Within the scope of each method optional substituents are used which are stable to the reaction conditions, or the functional groups which may participate in the reactions are present in protected form where necessary, and the removal of such protective groups is completed at appropriate stages by methods well known to those skilled in the art.

The compounds of this invention can be made according to conventional chemical methods, and/or as disclosed below, from starting materials which are either commercially available or producible according to routine, conventional chemical methods. General methods for the preparation of the compounds are given below, and the preparation of related compounds, is specifically illustrated in Examples.

Ureas of formula (I) can be prepared by a variety of simple methods known in the art. General approaches for the formation of those compounds can be found in "Advanced Organic Chemistry", by J. March, John Wiley and Sons, 1985 and in
5 "Comprehensive Organic Transformations", by R. C. Larock, VCH Publishers, 1989), which are hereby incorporated by reference.

More specifically, pyridine-1-oxides, quinoline-1-oxides and isoquinoline-1-oxides and their derivatives can be prepared from the corresponding pyridines, quinolines, and
10 isoquinolines using oxidation conditions known in the art. Some examples are as follows:

- peracids such as meta chloroperbenzoic acids in chlorinated solvents such as dichloromethane, dichloroethane, or chloroform (Markgraf et al., *Tetrahedron* 1991, 47, 183).
- (Me₃SiO)₂ in the presence of a catalytic amount of pertrhenic acid in chlorinated
15 solvents such as dichloromethane (Coperet et al., *Tetrahedron Lett.* 1998, 39, 761)
- Perfluoro-cis-2-butyl-3-propyloxaziridine in several combinations of halogenated solvents (Amone et al., *Tetrahedron* 1998, 54, 7831).
- Hypofluoric acid - acetonitrile complex in chloroform (Dayan et al., *Synthesis* 1999, 1427).
- 20 • Oxone, in the presence of a base such as KOH, in water (Robker et al., *J. Chem. Res., Synop.* 1993, 10, 412).
- Magnesium monoperoxyphthalate, in the presence of glacial acetic acid (Klemm et al., *J. Heterocyclic Chem.* 1990, 6, 1537).
- Hydrogen peroxide, in the presence of water and acetic acid (Lin A.J., *Org. Prep. Proced. Int.* 1991, 23(1), 114).
- 25 • Dimethyldioxirane in acetone (Boyd et al., *J. Chem. Soc., Perkin Trans.* 1991, 2, 2189).

The starting materials for the above mentioned oxidation are bis aryl ureas, which
30 contain either a pyridine, quinoline, or isoquinoline in one of their side chains. Specific preparations of these ureas are already described in the patent literature, and can be

adapted to the compounds of the present invention. For example, Miller S. et al, "Inhibition of p38 Kinase using Symmetrical and Unsymmetrical Diphenyl Ureas" *PCT Int. Appl.* WO 99 32463, Miller, S et al. "Inhibition of raf Kinase using Symmetrical and Unsymmetrical Substituted Diphenyl Ureas" *PCT Int. Appl.*, WO 99 32436, Dumas, J. et al., "Inhibition of p38 Kinase Activity using Substituted Heterocyclic Ureas" *PCT Int. Appl.*, WO 99 32111, Dumas, J. et al., "Method for the Treatment of Neoplasm by Inhibition of raf Kinase using N-Heteroaryl-N'-(hetero)arylureas" *PCT Int. Appl.*, WO 99 32106, Dumas, J. et al., "Inhibition of p38 Kinase Activity using Aryl- and Heteroaryl-Substituted Heterocyclic Ureas" *PCT Int. Appl.*, WO 99 32110, Dumas, J., et al., "Inhibition of raf Kinase using Aryl- and Heteroaryl- Substituted Heterocyclic Ureas" *PCT Int. Appl.*, WO 99 32455, Riedl, B., et al., "O-Carboxy Aryl Substituted Diphenyl Ureas as raf Kinase Inhibitors" *PCT Int. Appl.*, WO 00 42012, Riedl, B., et al., "O-Carboxy Aryl Substituted Diphenyl Ureas as p38 Kinase Inhibitors" *PCT Int. Appl.*, WO 00 41698.

The following copending U.S. applications are directed to diaryl ureas that find use in the treatment of raf and/or p38 mediated diseases and describe the preparation of specific diaryl ureas that are precursors to the compounds of this invention.

08/863,022, filed May 23, 1997;
08/996,344, filed December 22, 1997;
08/996,343, filed December 22, 1997;
08/996,181, filed December 22, 1997;
08/995,749, filed December 22, 1997;
08/995,750, filed December 22, 1997;
08/995,751, filed December 22, 1997;
09/083,399, filed May 22, 1998;
09/425,228, filed October 22, 1999;
09/777,920, filed February 7, 2001.
09/838,285, filed April 20, 2001;
09/838,286, filed April 20, 2001;

These applications are incorporated herein by reference.

The following published PCT applications are directed to diaryl ureas that find use in the treatment of p38 mediated diseases and also describe the preparation of specific diaryl ureas that are precursors to the compounds of this invention.

5 WO 99/23091;
WO 00/43384;
WO 00/55152;
WO 00/55139 and
WO 01/36403.

10 These applications are also incorporated herein by reference.

The invention also includes pharmaceutical compositions including a compound of this invention, and a physiologically acceptable carrier.

15 The compounds may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations. The term 'administration by injection' includes intravenous, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active
20 ingredients.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of
25 diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate;
30 granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be

uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already

mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, e.g.,
5 oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations.
10 These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis
15 oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for
20 example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a
25 demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the
30 rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

For all regimens of use disclosed herein for compounds of Formula I, the daily oral dosage regimen will preferably be from 0.01 to 200 mg / kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg / kg of total body weight. The daily rectal dosage regime will preferably be from 0.01 to 200 mg / kg of total body weight. The daily topical dosage regime will preferably be from 0.1 to 200 mg administered between one to four times daily. The daily inhalation dosage regime will preferably be from 0.01 to 10 mg / kg of total body weight. These dosages can be achieved with multiple dosages within a day or extended dosages (weekly/monthly).

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be appreciated by one skilled in the art that the specific dose level for a given patient depends on a variety of factors, including specific activity of the compound administered, age, body weight, health, sex, diet, time and route of administration, rate of excretion, etc. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of this invention given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the condition undergoing therapy.

The compounds can be produced from known compounds (or from starting materials which, in turn, can be produced from known compounds), e.g., through the

general preparative methods shown below. The activity of a given compound to inhibit raf kinase can be routinely assayed, e.g., according to procedures disclosed below.

5 The entire enclosure of all applications, patents and publications cited above and below are hereby incorporated by reference, including non-provisional application Serial No. 09/425,228 filed October 22, 1999, Serial No. 09/722,418 filed November 28, 2000 and Serial number (attorney docket number: Bayer 34 V1), filed December 3, 2001.

10 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples are, therefore, to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

EXAMPLES

15

All reactions are performed in flame-dried or oven-dried glassware under a positive pressure of dry argon or dry nitrogen, and are stirred magnetically unless otherwise indicated. Sensitive liquids and solutions are transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Unless otherwise
20 stated, the term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mmHg. Unless otherwise stated, the term 'under high vacuum' refers to a vacuum of 0.4 – 1.0 mmHg.

25 All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by weight. Commercial grade reagents and solvents are used without further purification.

30 Thin-layer chromatography (TLC) is performed using Whatman® pre-coated glass-backed silica gel 60A F-254 250 µm plates. Visualization of plates is effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in

ethanol followed by heating, (d) immersion of the plate in a cerium sulfate solution followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of 2,4-dinitrophenylhydrazine followed by heating. Column chromatography (flash chromatography) is performed using 230-400 mesh EM Science[®] silica gel.

5

Melting points (mp) are determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier transform infrared spectra are obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (¹H) nuclear magnetic resonance (NMR) are measured with a
10 General Electric GN-Omega 300 (300 MHz) spectrometer with either Me₄Si (δ 0.00) or residual protonated solvent (CHCl₃ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (¹³C) NMR spectra are measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent (CDCl₃ δ 77.0; MeOD-d₃; δ 49.0; DMSO-d₆ δ 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS)
15 are either obtained as electron impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) are obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Vacumetrics Desorption Chemical Ionization Probe for sample introduction. The ion source is maintained at 250 °C. Electron impact ionization is performed with electron energy of 70 eV and a trap current
20 of 300 μA. Liquid-caesium secondary ion mass spectra (FAB-MS), an updated version of fast atom bombardment is obtained using a Kratos Concept 1-H spectrometer. Chemical ionization mass spectra (CI-MS) are obtained using a Hewlett Packard MS-Engine (5989A) with methane or ammonia as the reagent gas (1x10⁻⁴ torr to 2.5x10⁻⁴ torr). The direct insertion desorption chemical ionization (DCI) probe (Vacumetrics, Inc.) is
25 ramped from 0-1.5 amps in 10 sec and held at 10 amps until all traces of the sample disappeared (~1-2 min). Spectra are scanned from 50-800 amu at 2 sec per scan. HPLC - electrospray mass spectra (HPLC ES-MS) are obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a C-18 column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra are
30 scanned from 120-800 amu using a variable ion time according to the number of ions in the source. Gas chromatography - ion selective mass spectra (GC-MS) is obtained with a

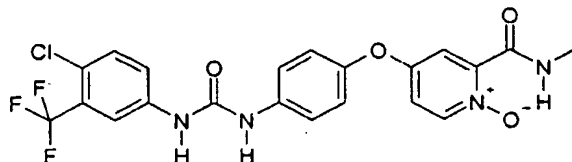
Hewlett Packard 5890 gas chromatograph equipped with an HP-1 methyl silicone column (0.33 mM coating; 25 m x 0.2 mm) and a Hewlett Packard 5971 Mass Selective Detector (ionization energy 70 eV). Elemental analyses are conducted by Robertson Microлит Labs, Madison NJ.

5

EXPERIMENTAL SYNTHESIS 1

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl} urea

10



15

The title compound is not a compound of this invention, and has been distinguished from the compounds of this invention by a proviso. However, its preparation illustrates how other compounds of the present invention can be prepared. The oxidation method exemplified herein can easily be adapted to the compounds of the present invention by those skilled in the art.

20

To a stirred mixture of N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} urea (500 mg, 1.08 mmol), in a mixture of anhydrous CH_2Cl_2 (2.2 mL) and anhydrous THF (2.2 mL) was added 3-chloroperbenzoic acid (77% pure, 1.09 g, 4.86 mmol, 4.5 equiv.), and the resulting mixture was heated at 40°C for 33 h. The resulting mixture was concentrated under reduced pressure, and the crude product was purified by MPLC (Biotage®; gradient from 20% acetone / hexane to 50% acetone / hexane). Recrystallization from EtOAc afforded N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl} urea as a white solid (293 mg, 57%); mp (uncorrected) 232-234°C; TLC (50% acetone/hexane) R_f 0.13; $^1\text{H-NMR}$ (DMSO- d_6) δ 11.48 (broad s, 1H), 9.19 (s, 1H), 8.98 (s, 1H), 8.38 (d, J = 5.8 Hz, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.64 (dd, J = 8.2 Hz, 2.6 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.57

25

(d, J = 8.7 Hz, 2H), 7.54 (d, J = 2.6 Hz, 1H), 7.28 (dd, J = 5.7 Hz, 2.5 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 2.86 (d, J = 5.0 Hz, 3H); HPLC EI-MS m/z 481 ((M+H)⁺). Anal. calcd for C₂₁H₁₆ClFN₄O₄: C 52.46% H 3.33% N 11.65%. Found: C 52.22% H 3.39% N 11.49%.

5

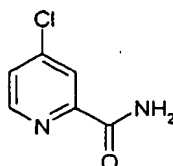
EXPERIMENTAL SYNTHESIS 2

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-yridyloxy)]phenyl} urea.

- 10 The title compound is not a compound of this invention. It has been distinguished from the compounds of this invention by a proviso. However, its preparation illustrates how other compounds of the present invention can be prepared.

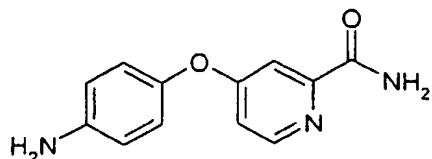
Step 1: Preparation of 4-chloro-2-pyridinecarboxamide

15



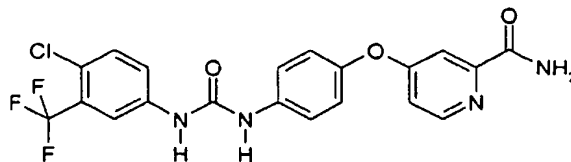
- To a stirred mixture of methyl 4-chloro-2-pyridinecarboxylate hydrochloride (1.0 g, 4.81 mmol) dissolved in conc. aqueous ammonia (32 mL) was added ammonium chloride (96.2 mg, 1.8 mmol, 0.37 equiv.), and the heterogeneous reaction mixture was stirred at ambient temperature for 16h. The reaction mixture was poured into EtOAc (500 mL) and water (300 mL). The organic layer was washed with water (2 x 300 mL) and a saturated NaCl solution (1 x 300 mL), dried (MgSO₄), concentrated in *vacuo* to give 4-chloro-2-pyridinecarboxamide as a beige solid (604.3 mg, 80.3%): TLC (50% EtOAc / hexane) R_f 0.20; ¹H-NMR (DMSO-d₆) δ 8.61 (d, J = 5.4 Hz, 1H), 8.20 (broad s, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.81 (broad s, 1H), 7.76 to 7.73 (m, 1H).

Step 2: Preparation of 4-(4-aminophenoxy)-2-pyridinecarboxamide



To 4-aminophenol (418 mg, 3.83 mmol) in anhydrous DMF (7.7 mL) was added
 5 potassium *tert*-butoxide (447 mg, 3.98 mmol, 1.04 equiv.) in one portion. The reaction
 mixture was stirred at room temperature for 2 h, and a solution of 4-chloro-2-
 pyridinecarboxamide (600 mg, 3.83 mmol, 1.0 equiv.) in anhydrous DMF (4 mL) was then
 added. The reaction mixture was stirred at 80 °C for 3 days and poured into a mixture of
 EtOAc and a saturated NaCl solution. The organic layer was sequentially washed with a
 10 saturated NH₄Cl solution then a saturated NaCl solution, dried (MgSO₄), and
 concentrated under reduced pressure. The crude product was purified using MPLC
 chromatography (Biotage®; gradient from 100% EtOAc to followed by 10% MeOH /
 50% EtOAc / 40% hexane) to give the 4-chloro-5-trifluoromethylaniline as a brown solid
 (510 mg, 58%). ¹H-NMR (DMSO-d₆) δ 8.43 (d, J = 5.7 Hz, 1H), 8.07 (br s, 1H), 7.66 (br
 15 s, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.07 (dd, J = 5.7 Hz, 2.7 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2
 H), 6.62 (d, J = 8.7 Hz, 2H), 5.17 (broad s, 2H); HPLC EI-MS *m/z* 230 ((M+H)⁺).

Step 3: Preparation of N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-
 pyridyloxy)]phenyl} urea

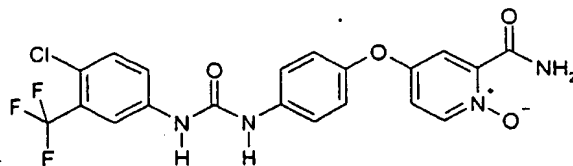


20

A mixture of 4-chloro-5-trifluoromethylaniline (451 mg, 2.31 mmol, 1.1 equiv.)
 and 1,1'-carbonyl diimidazole (419 mg, 2.54 mmol, 1.2 equiv.) in anhydrous dichloroethane
 (5.5 mL) was stirred under argon at 65 °C for 16 h. Once cooled to room temperature, a
 25 solution of 4-(4-aminophenoxy)-2-pyridinecarboxamide (480 mg, 2.09 mmol) in anhydrous
 THF (4.0 mL) was added, and the reaction mixture was stirred at 60 °C for 4 h. The

reaction mixture was poured into EtOAc, and the organic layer was washed with water (2x) and a saturated NaCl solution (1x), dried (MgSO₄), filtered, and evaporated in *vacuo*. Purification using MPLC chromatography (Biotage®; gradient from 100% EtOAc to 2% MeOH / EtOAc) gave N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea as a white solid (770 mg, 82%): TLC (EtOAc) R_f 0.11, 100% ethyl acetate ¹H-NMR (DMSO-d₆) δ 9.21 (s, 1H), 8.99 (s, 1H), 8.50 (d, J = 5.6 Hz, 1H), 8.11 (s, 1H), 8.10 (s, 1H), 7.69 (broad s, 1H), 7.64 (dd, J = 8.2 Hz, 2:1 Hz, 1H), 7.61 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 2.5 Hz, 1H), 7.15 (d, J = 8.9 Hz, 2H), 7.14 (m, 1H); MS LC-MS (MH⁺ = 451). Anal. calcd for C₂₀H₁₄ClF₃N₄O₃: C 53.29% H 3.13% N 12.43%. Found: C 53.33% H 3.21% N 12.60%;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea



15

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea (125.6 mg, 51%) was prepared as a white solid from N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea (240.0 mg, 0.53 mmol), in the manner described for N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl} urea: TLC (5% MeOH / CH₂Cl₂) R_f 0.17; ¹H-NMR (DMSO-d₆) δ 10.72 (d, J = 4.3 Hz, 1H), 9.21 (s, 1H), 8.99 (s, 1H), 8.36 (d, J = 7.2 Hz, 1H), 8.31 (d, J = 4.1 Hz, 1H), 8.10 (d, J = 2.3 Hz, 1H), 7.65 (dd, J = 8.7 Hz, 2.3 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.57 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 3.8 Hz, 1H), 7.28 (dd, J = 7.2 Hz, 3.8 Hz, 1H), 7.18 (d, J = 9.0 Hz, 2H); HPLC EI-MS *m/z* 467 ((M+H)⁺); Anal. calcd for C₂₀H₁₄ClF₃N₄O₄ 0.5H₂O: C 50.49% H 3.18% N 11.78%. Found: C 50.69% H 2.86% N 11.47%.

BIOLOGICAL EXAMPLES

P38 Kinase *in vitro* Assay:

The *in vitro* inhibitory properties of compounds are determined using a p38 kinase inhibition assay. P38 activity is detected using an *in vitro* kinase assay run in 96-well microtiter plates. Recombinant human p38 (0.5 µg/mL) is mixed with substrate (myelin basic protein, 5 µg/mL) in kinase buffer (25 mM Hepes, 20 mM MgCl₂ and 150 mM NaCl) and compound. One µCi/well of ³³P-labeled ATP (10 µM) is added to a final volume of 100 µL. The reaction is run at 32 °C for 30 min. and stopped with a 1M HCl solution. The amount of radioactivity incorporated into the substrate is determined by trapping the labeled substrate onto negatively charged glass fiber filter paper using a 1% phosphoric acid solution and read with a scintillation counter. Negative controls include substrate plus ATP alone.

LPS Induced TNFα Production in Mice:

The *in vivo* inhibitory properties of selected compounds can be determined using a murine LPS induced TNFα production *in vivo* model. BALB/c mice (Charles River Breeding Laboratories; Kingston, NY) in groups of ten are treated with either vehicle or compound by the route noted. After one hour, endotoxin (E. coli lipopolysaccharide (LPS) 100 µg) is administered intraperitoneally (i.p.). After 90 min, animals are euthanized by carbon dioxide asphyxiation and plasma is obtained from individual animals by cardiac puncture into heparinized tubes. The samples are clarified by centrifugation at 12,500 x g for 5 min at 4 °C. The supernatants are decanted to new tubes, which are stored as needed at -20 °C. TNFα levels in sera are measured using a commercial murine TNF ELISA kit (Genzyme).

The two preceding biological examples can be used to demonstrate that the compounds are inhibiting p38 kinase *in vitro* and *in vivo*, and therefore establishes their utility in the treatment of p38 mediated diseases, such as inflammation and osteoporosis.

In Vitro raf Kinase Assay:

In an *in vitro* kinase assay, raf is incubated with MEK in 20 mM Tris-HCl, pH 8.2 containing 2 mM 2-mercaptoethanol and 100 mM NaCl. This protein solution (20 μ L) is mixed with water (5 μ L) or with compounds diluted with distilled water from 10 mM stock solutions of compounds dissolved in DMSO. The kinase reaction is initiated by adding 25 μ L [γ - 33 P]ATP (1000-3000 dpm/pmol) in 80 mM Tris-HCl, pH 7.5, 120 mM NaCl, 1.6 mM DTT, 16 mM $MgCl_2$. The reaction mixtures are incubated at 32 $^{\circ}C$, usually for 22 min. Incorporation of ^{33}P into protein is assayed by harvesting the reaction onto phosphocellulose mats, washing away free counts with a 1% phosphoric acid solution and quantitating phosphorylation by liquid scintillation counting. For high throughput screening, 10 μ M ATP and 0.4 μ M MEK are used. In some experiments, the kinase reaction is stopped by adding an equal amount of Laemmli sample buffer. Samples are boiled 3 min and the proteins resolved by electrophoresis on 7.5% Laemmli gels. Gels are fixed, dried and exposed to an imaging plate (Fuji). Phosphorylation is analyzed using a Fujix Bio-Imaging Analyzer System.

15

Tumor cell proliferation assay:

For *in vitro* growth assay, human tumor cell lines, including but not limited to HCT116 and DLD-1, containing mutated K-ras genes are used in standard proliferation assays for anchorage dependent growth on plastic or anchorage independent growth in soft agar. Human tumor cell lines are obtained from ATCC (Rockville MD) and maintained in RPMI with 10% heat inactivated fetal bovine serum and 200 mM glutamine. Cell culture media and additives are obtained from Gibco/BRL (Gaithersburg, MD) except for fetal bovine serum (JRH Biosciences, Lenexa, KS). In a standard proliferation assay for anchorage dependent growth, 3×10^3 cells are seeded into 96-well tissue culture plates and allowed to attach overnight at 37 $^{\circ}C$ in a 5% CO_2 incubator. Compounds are titrated in media in dilution series and added to 96 well cell cultures. Cells are allowed to grow 5 days typically with a feeding of fresh compound containing media on day three. Proliferation is monitored by measuring metabolic activity with standard XTT colorimetric assay (Boehringer Mannheim) measured by standard ELISA plate reader at OD 490/560, harvesting the cells onto glass fiber mats using a cell harvester and measuring 3H -thymidine incorporation by liquid scintillant counting.

30

For anchorage independent cell growth, cells are plated at 1×10^3 to 3×10^3 in 0.4% Seaplaque agarose in RPMI complete media, overlaying a bottom layer containing only 0.64% agar in RPMI complete media in 24-well tissue culture plates. Complete media plus dilution series of compounds are added to wells and incubated at 37 °C in a 5% CO₂ incubator for 10-14 days with repeated feedings of fresh media containing compound at 3-4 day intervals. Colony formation is monitored and total cell mass, average colony size and number of colonies are quantitated using image capture technology and image analysis software (Image Pro Plus, media Cybernetics).

The two preceding assays establish that the compounds of Formula I are active to inhibit raf kinase activity and to inhibit oncogenic cell growth.

KDR (VEGFR2) Assay:

The cytosolic kinase domain of KDR kinase is expressed as a 6His fusion protein in Sf9 insect cells. The KDR kinase domain fusion protein is purified over a Ni⁺⁺ chelating column. Ninety-six well ELISA plates are coated with 5 µg poly(Glu4;Tyr1) (Sigma Chemical Co., St Louis, MO) in 100 µl HEPES buffer (20 mM HEPES, pH 7.5, 150 mM NaCl, 0.02% Thimerosal) at 4° overnight. Before use, the plate is washed with HEPES, NaCl buffer and the plates are blocked with 1% BSA, 0.1% Tween 20 in HEPES, NaCl buffer.

Test compounds are serially diluted in 100% DMSO from 4 mM to 0.12 µM in half-log dilutions. These dilutions are further diluted twenty fold in H₂O to obtain compound solutions in 5% DMSO. Following loading of the assay plate with 85 µl of assay buffer (20 mM HEPES, pH 7.5, 100 mM KCl, 10 mM MgCl₂, 3 mM MnCl₂, 0.05% glycerol, 0.005% Triton X-100, 1 mM -mercaptoethanol, with or without 3.3 µM ATP), 5 µl of the diluted compounds are added to a final assay volume of 100 µl. Final concentrations are between 10 µM, and 0.3 nM in 0.25% DMSO. The assay is initiated by the addition of 10µl (30 ng) of KDR kinase domain.

The assay is incubated with test compound or vehicle alone with gentle agitation at room temperature for 60 minutes. The wells are washed and phosphotyrosines (PY) are probed

with an anti-phosphotyrosine (PY), mAb clone 4G10 (Upstate Biotechnology, Lake Placid, NY). PY/anti-PY complexes are detected with an anti-mouse IgG/HRP conjugate (Amersham International plc, Buckinghamshire, England). Phosphotyrosine is quantitated by incubating with 100 µl 3, 3', 5, 5' tetramethylbenzidine solution
5 (Kirkegaard and Perry, TMB Microwell 1 Component peroxidase substrate). Color development is arrested by the addition of 100 µl 1% HCl-based stop solution (Kirkegaard and Perry, TMB 1 Component Stop Solution).

Optical densities are determined spectrophotometrically at 450 nm in a 96-well plate reader, SpectraMax 250 (Molecular Devices). Background (no ATP in assay) OD values
10 are subtracted from all ODs and the percent inhibition is calculated according to the equation:

$$\% \text{ Inhibition} = \frac{(\text{OD}(\text{vehicle control}) - \text{OD}(\text{with compound})) \times 100}{\text{OD}(\text{vehicle control}) - \text{OD}(\text{no ATP added})}$$

15

The IC₅₀ values are determined with a least squares analysis program using compound concentration versus percent inhibition.

Cell mechanistic assay-Inhibition of 3T3 KDR phosphorylation:

20 NIH3T3 cells expressing the full length KDR receptor are grown in DMEM (Life Technologies, Inc., Grand Island, NY) supplemented with 10% newborn calf serum, low glucose, 25 mM /L sodium pyruvate, pyridoxine hydrochloride and 0.2 mg/ ml of G418 (Life Technologies Inc., Grand Island, NY). The cells are maintained in collagen I-coated T75 flasks (Becton Dickinson Labware, Bedford, MA) in a humidified 5% CO₂
25 atmosphere at 37°C.

Fifteen thousand cells are plated into each well of a collagen I-coated 96-well plate in the DMEM growth medium. Six hours later, the cells are washed and the medium is replaced with DMEM without serum. After overnight culture to quiesce the cells, the medium is replaced by Dulbecco's phosphate-buffered saline (Life Technologies Inc.,
30 Grand Island, NY) with 0.1% bovine albumin (Sigma Chemical Co., St Louis, MO).

After adding various concentrations (0-300 nM) of test compounds to the cells in 1% final concentration of DMSO, the cells are incubated at room temperature for 30 minutes. The cells are then treated with VEGF (30 ng / ml) for 10 minutes at room temperature. Following VEGF stimulation, the buffer is removed and the cells are lysed by addition of
5 150 µl of extraction buffer (50 mM Tris, pH 7.8, supplemented with 10% glycerol, 50 mM BGP, 2 mM EDTA, 10 mM NaF, 0.5 mM NaVO₄, and 0.3% TX-100) at 4°C for 30 minutes.

To assess receptor phosphorylation, 100 microliters of each cell lysate is added to the wells of an ELISA plate precoated with 300 ng of antibody C20 (Santa Cruz
10 Biotechnology, Inc., Santa Cruz , CA). Following a 60-minute incubation, the plate is washed and bound KDR is probed for phosphotyrosine using an anti-phosphotyrosine mAb clone 4G10 (Upstate Biotechnology, Lake Placid, NY). The plate is washed and wells are incubated with anti-mouse IgG/HRP conjugate (Amersham International plc, Buckinghamshire, England) for 60 minutes. Wells are washed and phosphotyrosine is
15 quantitated by addition of 100 µl per well of 3,3',5,5' tetramethylbenzidine (Kirkegaard and Perry, TMB Microwell 1 Component peroxidase substrate) solution. Color development is arrested by the addition of 100 µl 1% HCl based stop solution (Kirkegaard and Perry, TMB 1 Component Stop Solution).

Optical densities (OD) are determined spectrophotometrically at 450 nm in a 96-well
20 plate reader (SpectraMax 250, Molecular Devices). Background (no VEGF added) OD values are subtracted from all ODs and percent inhibition is calculated according to the equation:

$$\% \text{ Inhibition} = \frac{(\text{OD(VEGF control)} - \text{OD(with test compound)}) \times 100}{\text{OD(VEGF control)} - \text{OD(no VEGF added)}}$$

25

IC₅₀s are determined on some of the exemplary materials with a least squares analysis program using compound concentration versus percent inhibition.

In vivo assay of VEGFR inhibition: Matrigel® Angiogenesis Model:

Preparation of Matrigel Plugs and *in vivo* Phase: Matrigel® (Collaborative Biomedical Products, Bedford, MA) is a basement membrane extract from a murine tumor composed primarily of laminin, collagen IV and heparan sulfate proteoglycan. It is provided as a sterile liquid at 4° C, but rapidly forms a solid gel at 37° C.

Liquid Matrigel at 4° C is mixed with SK-MEL2 human tumor cells that are transfected with a plasmid containing the murine VEGF gene with a selectable marker. Tumor cells are grown *in vitro* under selection and cells are mixed with cold liquid Matrigel at a ratio of 2×10^6 per 0.5 ml. One half milliliter is implanted subcutaneously near the abdominal midline using a 25 gauge needle. Test compounds are dosed as solutions in Ethanol/Cremaphor EL/saline (12.5%:12.5%:75%) at 30, 100, and 300 mg/kg po once daily starting on the day of implantation. Mice are euthanized 12 days post-implantation and the Matrigel pellets are harvested for analysis of hemoglobin content.

Hemoglobin Assay: the Matrigel pellets are placed in 4 volumes (w/v) of 4° C Lysis Buffer (20mM Tris pH 7.5, 1mM EGTA, 1mM EDTA, 1% Triton X-100 [EM Science, Gibbstown, N.J.], and complete, EDTA-free protease inhibitor cocktail [Mannheim, Germany]), and homogenized at 4°C. Homogenates are incubated on ice for 30 minutes with shaking and centrifuged at 14K x g for 30 minutes at 4° C. Supernatants are transferred to chilled microfuge tubes and stored at 4° C for hemoglobin assay.

Mouse hemoglobin (Sigma Chemical Co., St. Louis, MO) is suspended in autoclaved water (BioWhittaker, Inc, Walkersville, MD.) at 5 mg/ ml. A standard curve is generated from 500 micrograms/ml to 30 micrograms/ml in Lysis Buffer (see above). Standard curve and lysate samples are added at 5 microliters /well in duplicate to a polystyrene 96-well plate. Using the Sigma Plasma Hemoglobin Kit (Sigma Chemical Co., St. Louis, MO), TMB substrate is reconstituted in 50 mls room temperature acetic acid solution. One hundred microliters of substrate is added to each well, followed by 100 microliters /well of Hydrogen Peroxide Solution at room temperature. The plate is incubated at room temperature for 10 minutes.

Optical densities are determined spectrophotometrically at 600 nm in a 96-well plate reader, SpectraMax 250 Microplate Spectrophotometer System (Molecular Devices, Sunnyvale, CA). Background Lysis Buffer readings are subtracted from all wells.

Total sample hemoglobin content is calculated according to the following equation:

$$\text{Total Hemoglobin} = (\text{Sample Lysate Volume}) \times (\text{Hemoglobin Concentration})$$

- 5 The average Total Hemoglobin of Matrigel samples without cells is subtracted from each Total Hemoglobin Matrigel sample with cells. Percent inhibition is calculated according to the following equation:

$$\begin{aligned} 10 \quad \% \text{ Inhibition} = & \frac{(\text{Average Total Hemoglobin Drug-Treated Tumor Lysates}) \times 100}{(\text{Average Total Hemoglobin Non-Treated Tumor Lysates})} \end{aligned}$$

The three preceding assays establish that the compounds of Formula I are active to inhibit VEGF receptor kinase activity and to inhibit angiogenesis.

15

***In Vivo* Assay of antitumor activity:**

- An *in vivo* assay of the inhibitory effect of the compounds on tumors (e.g., solid cancers) mediated by raf kinase can be performed as follows: CDI nu/nu mice (6-8 weeks old) are injected subcutaneously into the flank at 1×10^6 cells with human colon adenocarcinoma cell line. The mice are dosed i.p., i.v. or p.o. at 10, 30, 100, or 300 mg/Kg beginning on approximately day 10, when tumor size is between 50-100 mg. Animals are dosed for 14 consecutive days; tumor size is monitored with calipers twice a week. The inhibitory effect of the compounds on p38, raf and VEGFR kinases and therefore on tumor growth (e.g., solid cancers) can further be demonstrated *in vivo* according to the technique of Monia et al. (*Nat. Med.* 1996, 2, 668-75).
- 20
25

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

30

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various conditions and usages.

5

10

15

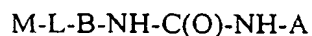
20

25

30

What is claimed is:

1. A compound of formula (I) or a salt, prodrug or isolated stereoisomer thereof



I

5

wherein A is selected from the group consisting of:

- (i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, COR^1 , COOR^1 , CONR^1R^2 , $\text{NR}^1\text{C(O)R}^2$, halogen, cyano, and nitro;
- 10 (ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, COR^1 , COOR^1 , CONR^1R^2 , $\text{NR}^1\text{C(O)R}^2$, halogen, cyano, and nitro;
- (iii) 5 and 6 membered monocyclic heteroaryl, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3
- 15 substituents independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, COR^1 , COOR^1 , CONR^1R^2 , NR^1COR^2 , halogen, cyano, and nitro; and
- (iv) 8-10 membered bicyclic heteroaryl, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents
- 20 independently selected from the group consisting of R^1 , OR^1 , NR^1R^2 , $\text{S(O)}_q\text{R}^1$, $\text{SO}_2\text{NR}^1\text{R}^2$, $\text{NR}^1\text{SO}_2\text{R}^2$, COR^1 , COOR^1 , CONR^1R^2 , NR^1COR^2 , halogen, cyano, and nitro;

B is selected from the group consisting of :

- (i) phenylene, optionally substituted with 1-3 substituents independently selected from the group consisting of $\text{C}_1\text{-C}_5$ linear or branched alkyl, $\text{C}_1\text{-C}_5$ linear or branched
- 25 haloalkyl, $\text{C}_1\text{-C}_3$ alkoxy, hydroxy, amino, $\text{C}_1\text{-C}_3$ alkylamino, $\text{C}_1\text{-C}_3$ dialkylamino, halogen, cyano, and nitro;
- (ii) naphthylene, optionally substituted with 1-3 substituents independently selected from the group consisting of $\text{C}_1\text{-C}_5$ linear or branched alkyl, $\text{C}_1\text{-C}_5$ linear or branched
- haloalkyl, $\text{C}_1\text{-C}_3$ alkoxy, hydroxy, amino, $\text{C}_1\text{-C}_3$ alkylamino, $\text{C}_1\text{-C}_3$ dialkylamino,
- 30 halogen, cyano, and nitro;

- (iii) 5 and 6 membered monocyclic heteroaryl-ene, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched haloalkyl, C₁-C₃ alkoxy, hydroxy, amino, C₁-C₃ alkylamino, C₁-C₃ dialkylamino, halogen, cyano, and nitro; and
- (iv) 8-10 membered bicyclic heteroaryl-ene, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched haloalkyl, C₁-C₃ alkoxy, hydroxy, amino, C₁-C₃ alkylamino, C₁-C₃ dialkylamino, halogen, cyano, and nitro;

L is selected from the group consisting of :

- (a) $-(CH_2)_m-O-(CH_2)_l-$,
 (b) $-(CH_2)_m-(CH_2)_l-$,
 (c) $-(CH_2)_m-C(O)-(CH_2)_l-$,
 15 (d) $-(CH_2)_m-NR^{3a}-(CH_2)_l-$,
 (e) $-(CH_2)_m-NR^{3a}C(O)-(CH_2)_l-$,
 (f) $-(CH_2)_m-S-(CH_2)_l-$,
 (g) $-(CH_2)_m-C(O)NR^{3a}-(CH_2)_l-$,
 (h) $-(CH_2)_m-CF_2-(CH_2)_l-$,
 20 (i) $-(CH_2)_m-CCl_2-(CH_2)_l-$,
 (j) $-(CH_2)_m-CHF-(CH_2)_l-$,
 (k) $-(CH_2)_m-CR^{3a}(OH)-(CH_2)_l-$,
 (l) $-(CH_2)_m-C\equiv C-(CH_2)_l-$,
 (m) $-(CH_2)_m-C=C-(CH_2)_l-$,
 25 (n) a single bond; and
 (o) $-(CH_2)_m-CR^{3a}R^{3b}-(CH_2)_l-$;

wherein m and l are integers independently selected from 0-4;

M is selected from the group consisting of :

(a) pyridine-1-oxide substituted 1 to 3 times by a substituent selected from the group consisting of $-C(O)NR^4R^5$, $-C(NR^4)R^5$, $-C(O)R^4$, $-SO_2R^4$, and $-SO_2NR^4R^5$; which is optionally additionally substituted by Z_r ;

(b) quinoline-1-oxide, which is optionally substituted by Z_n ; and

5 (c) isoquinoline-1-oxide, which is optionally substituted by Z_n ;

wherein r is 0-2, n is 0-3, and each Z is independently selected from the group consisting of R^4 , halogen, cyano, $-CO_2R^4$, $-C(O)R^4$, $-C(O)NR^4R^5$, $-NO_2$, $-OR^4$, $-NR^4R^5$, $-NR^4C(O)OR^5$, $-NR^4C(O)R^5$, $-S(O)_pR^4$, and $-SO_2NR^4R^5$

wherein each R^1 , R^2 , R^4 and R^5 is independently selected from the group
10 consisting of:

(a) hydrogen,

(b) C_1 - C_5 linear, branched, or cyclic alkyl,

(c) phenyl,

(d) 5-6 membered monocyclic heteroaryl heteroaryl having 1-4 heteroatoms selected
15 from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S,

(e) C_1 - C_3 alkyl-phenyl,

(f) C_1 - C_3 alkyl heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, said heteroaryl including 5-6 membered monocyclic and 8-10 membered
20 bicyclic heteroaryl, and

(g) up to per-halo substituted C_1 - C_5 linear or branched alkyl; and

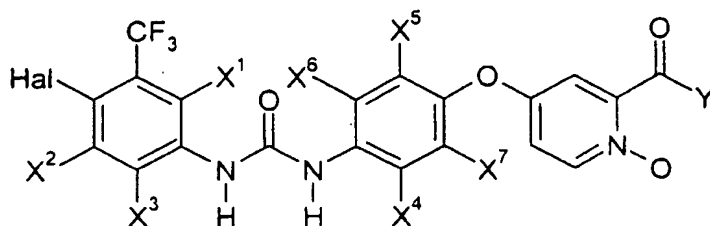
wherein each R^1 , R^2 , R^4 and R^5 , when not hydrogen or perhalo substituted C_1 - C_5 linear or branched alkyl, are optionally substituted with 1-3 substituents independently selected from the group consisting of C_1 - C_5 linear or branched alkyl, up to perhalo
25 substituted C_1 - C_5 linear or branched alkyl, C_1 - C_3 alkoxy, hydroxy, amino, C_1 - C_3 alkylamino, C_1 - C_6 dialkylamino, halogen, cyano, and nitro;

wherein each R^{3a} and R^{3b} is hydrogen or C_1 - C_5 linear or branched alkyl;

and p and q are integers each independently selected from 0, 1, or 2

subject to the proviso that formula I does not include compounds of formula II:

30



II

wherein,

- 5 Y is OR^1 or NHR^2 ,
 Hal is chlorine or bromine,
 R^1 is H or $\text{C}_1\text{-C}_6$ alkyl
 R^2 is H, OH, CH_3 or CH_2OH ,
 X^1 to X^7 are each, independently, H, OH or $\text{O}(\text{CO})\text{C}_1\text{-C}_4$ alkyl.

10

2. A compound as in claim 1 wherein A and B of formula I, are each independently:

- a substituted or unsubstituted phenyl group,
 a substituted or unsubstituted a naphthyl group,
 15 a substituted or unsubstituted monocyclic heteroaryl group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-triazinyl, 4-triazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,3-triazol-3-yl, 1,2,3-triazol-5-yl, 1-tetrazolyl, 5-tetrazolyl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,3,4-thiadiazol-3-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 3-pyridazinyl-, 4-pyridazinyl, 2-pyrazinyl and 3-pyrazinyl or

a substituted or unsubstituted bicyclic heteroaryl group selected from the group consisting of 2-, 3-, 4-, 5-, 6- and 7-benzofuryl, 2-, 3-, 4-, 5-, 6- and 7-benzothieryl, 1-, 2-, 3-, 4-, 5-, 6- and 7-indolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-isoindolyl, 1-, 2-, 4- and 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- and 7-indazolyl (benzopyrazolyl), 2-, 4-, 5-, 6- and 7-benzoxazolyl, 3-, 4-, 5- 6- and 7-benzisoxazolyl, 1-, 3-, 4-, 5-, 6- and 7-benzothiazolyl, 2-, 4-, 5-, 6- and 7-benzisothiazolyl, 2-, 4-, 5-, 6- and 7-benz-1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- and 8-quinoliny, 1-, 3-, 4-, 5-, 6-, 7-, 8- isoquinoliny, and 2-, 4-, 5-, 6-, 7- and 8-quinazoliny.

10

3. A compound as in claim 1 wherein A of formula I is

a substituted or unsubstituted phenyl group,

a substituted or unsubstituted a naphthyl group,

a substituted or unsubstituted monocyclic heteroaryl group selected from the group consisting of 2- furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-triazinyl, 4-triazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, , 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,3-triazol-3-yl, 1,2,3-triazol-5-yl, 1-tetrazolyl, 5-tetrazolyl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,3,4-thiadiazol-3-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 3-pyridazinyl-, 4-pyridazinyl, 2-pyrazinyl and 3-pyrazinyl or

a substituted or unsubstituted bicyclic heteroaryl group selected from the group consisting of 2-, 3-, 4-, 5-, 6- and 7-benzofuryl, 2-, 3-, 4-, 5-, 6- and 7-benzothieryl, 1-, 2-, 3-, 4-, 5-, 6- and 7-indolyl, 1-, 2-, 4- and 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- and 7-indazolyl (benzopyrazolyl), 2-, 4-, 5-, 6- and 7-benzoxazolyl, 3-, 4-, 5- 6- and 7-benzisoxazolyl, 1-, 3-, 4-, 5-, 6- and 7-benzothiazolyl, 2-, 4-, 5-, 6- and 7-

benzothiazolyl, 2-, 4-, 5-, 6- and 7-benz-1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- and 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, 8- isoquinolinyl, and 2-, 4-, 5-, 6-, 7- and 8-quinazolinyl and B of formula I is

a substituted or unsubstituted phenyl group,

5 a substituted or unsubstituted monocyclic heteroaryl group selected from the group consisting of 2- furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-triazinyl, 4-triazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 10 1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-yl, 1,2,3-triazol-3-yl, 1,2,3-triazol-5-yl, 1-tetrazolyl, 5-tetrazolyl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 15 1,3,4-thiadiazol-3-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 3-pyridazinyl-, 4-pyridazinyl, 2-pyrazinyl and 3-pyrazinyl or

a substituted or unsubstituted bicyclic heteroaryl group selected from the group consisting of 2-, 3-, 4-, 5-, 6- and 7-benzofuryl, 2-, 3-, 4-, 5-, 6- and 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- and 7-indolyl, 1-, 2-, 4- and 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- and 7-indazolyl (benzopyrazolyl), 2-, 4-, 5-, 6- and 7-benzoxazolyl, 3-, 4-, 5-, 6- and 7-benzisoxazolyl, 1-, 3-, 4-, 5-, 6- and 7-benzothiazolyl, 2-, 4-, 5-, 6- and 7-benzisothiazolyl, 2-, 4-, 5-, 6- and 7-benz-1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- and 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, 8- isoquinolinyl, and 2-, 4-, 5-, 6-, 7- and 8-quinazolinyl.

25

4. A compound as in claim 1 wherein

A of formula I is a substituted or unsubstituted group selected from the group consisting of phenyl, naphthyl, furyl, isoindolyl, oxadiazolyl, oxazolyl, isooxazolyl, 30 indolyl, indazolyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, pyrazolyl, pyridinyl,

pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiadiazolyl, thiazolyl and thienyl,

B of formula I is a substituted or unsubstituted group selected from the group consisting of phenylene, naphthylene, thienylene, furylene, pyridine-ene, quinoline-ene,
5 isoquinoline-ene and indole-ene,

L is selected from the group consisting of -CH₂O-, -OCH₂-, -O-, a single bond, -CH₂-, -NH-, -N(CH₃)-, -N(CH₃)CH₂-, -NC₂H₄-, -C(O)-, -NHCH₂-, -N(CH₃)C(O)-, -NHC(O)-, -CH₂N(CH₃)-, -C(O)NH-, -CH₂S-, -SCH₂-, -S-, -C(O)NCH₃-, -CH₂C(O)N(CH₃)-, -C(O)N(CH₃)CH₂-, -CF₂-, -CCl₂-, -CHF- and -CH(OH)-, and

10 M is defined as in claim 1.

5. A compound as in claim 1 wherein

A of formula I is a substituted or unsubstituted group selected from the group consisting of phenyl, naphthyl, furyl, isoindolyl, oxadiazolyl, oxazolyl, isoxazolyl,
15 indolyl, indazolyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiadiazolyl, thiazolyl and thienyl,

B of formula I is a substituted or unsubstituted group selected from the group consisting of phenylene, thienylene, furylene, pyridine-ene, quinoline-ene, isoquinoline-ene and indole-ene,
20

L is selected from the group consisting of -CH₂O-, -OCH₂-, -O-, a single bond, -CH₂-, -NH-, -N(CH₃)-, -N(CH₃)CH₂-, -NC₂H₄-, -C(O)-, -NHCH₂-, -N(CH₃)C(O)-, -NHC(O)-, -CH₂N(CH₃)-, -C(O)NH-, -CH₂S-, -SCH₂-, -S-, -C(O)NCH₃-, -CH₂C(O)N(CH₃)-, -C(O)N(CH₃)CH₂-, -CF₂-, -CCl₂-, -CHF- and -CH(OH)-, and

25 M is defined as in claim 1.

6. A compound as in claim 4 wherein

A of formula I is a substituted group and the substituents are selected from the group consisting of methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, i-propyl, t-butyl,
30 methylethyl, methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy,

propoxy, butyoxy, pentoxy, methyl sulfonyl, trifluoromethyl sulfonyl, Cl, Br, F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino.

7. A compound as in claim 1 wherein

5 A of formula I is a substituted or unsubstituted group selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, pyrazolyl, quinoliny, isoquinoliny, isoindolyl, pyrrolyl, indazolyl, thienyl, furyl and isoxazolyl and

B of formula I is a substituted or unsubstituted group selected from the group consisting of phenylene, naphthylene, thienylene, furylene, pyridine-ene, quinoline-ene, isoquinoline-ene and indole-ene.
10

8. A compound as in claim 1 wherein

A of formula I is a substituted or unsubstituted group selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, pyrazolyl, quinoliny, isoquinoliny, isoindolyl, pyrrolyl, indazolyl, thienyl, furyl and isoxazolyl and
15

B of formula I is a substituted or unsubstituted group selected from the group consisting of phenylene, thienylene, furylene, pyridine-ene, isoquinoline-ene and indole-ene.

9. A compound as in claim 1 wherein

20 A of formula I is a substituted or unsubstituted group selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, pyrazolyl, quinoliny, isoquinoliny, isoindolyl, pyrrolyl, indazolyl, thienyl, furyl and isoxazolyl and

B of formula I is a substituted or unsubstituted group selected from the group consisting of phenylene and pyridine-ene.

25

10. A compound as in claim 7 wherein

A of formula I is a substituted group and the substituents are selected from the group consisting of:

NH(C₁-C₅ alkyl, phenyl or pyridinyl);

30 N(C₁-C₅ alkyl)(C₁-C₅ alkyl, phenyl or pyridinyl);

S(O)₂ (C₁-C₅ alkyl);

SO₂NH(C₁-C₅ alkyl);
 SO₂N(C₁-C₅ alkyl)(C₁-C₅ alkyl);
 NHSO₂(C₁-C₅ alkyl);
 N(C₁-C₃ alkyl) SO₂(C₁-C₅ alkyl);
 5 CO(C₁-C₆ alkyl, phenyl or pyridinyl);
 COO(C₁-C₆ alkyl, phenyl or pyridinyl);
 COOH;
 CONH₂ ;
 CONH(C₁-C₆ alkyl, phenyl or pyridinyl);
 10 CON(C₁-C₆ alkyl, phenyl or pyridinyl);
 NHCO(C₁-C₅ alkyl, phenyl or pyridinyl) and
 N(C₁-C₅ alkyl)CO(C₁-C₅ alkyl).

15

11. A compound of formula I of claim 1 wherein in A, and B are one of the following combinations and M is as defined in claim 1:

A= phenyl, B=phenylene,
 A= phenyl, B=pyridinyl-ene,
 20 A= phenyl, B= isoquinolinyl-ene,
 A= pyridinyl, B=phenylene,
 A= pyridinyl, B=pyridinyl-ene,
 A= pyridinyl, B= isoquinolinyl-ene,
 A= naphthyl , B=phenylene,
 25 A= naphthyl , B=pyridinyl-ene,

 A= naphthyl , B= isoquinolinyl-ene,
 A= isoquinolinyl, B=phenylene,
 A= isoquinolinyl, B=pyridinyl-ene,
 30 A= isoquinolinyl, B= isoquinolinyl-ene,
 A=quinolinyl, B=phenylene,

- A=quinoliny, B=pyridinyl-ene,
A=quinoliny, B=isoquinoliny-ene,
A=pyrazolyl, B=phenylene,
A=pyrazolyl, B=pyridinyl-ene,
5 A=pyrazolyl, B=isoquinoliny-ene,
A=isoxazolyl, B=phenylene,
A=isoxazolyl, B=pyridinyl-ene,
A=isoxazolyl, B=isoquinoliny-ene.
A=indazolyl, B=phenylene,
10 A=indazolyl, B=pyridinyl-ene,
and
A=indazolyl, B=isoquinoliny-ene.
- 15 12. A pharmaceutical composition comprising
a) one or more compounds of formula I of claim 1, or a isolated stereoisomer, a
pharmaceutically acceptable salt, or a prodrug of a compound of formula (I) and
b) at least one pharmaceutically acceptable carrier.
- 20 13. A pharmaceutical composition comprising
a) one or more compounds of formula I of claim 1, or a salt, prodrug or isolated
stereoisomer of a compound of formula I,
b) at least one other cytotoxic or cytostatic chemotherapeutic agent, wherein the
25 amounts of a) and b) are jointly effective for treating a cancer, and
c) at least one pharmaceutically acceptable carrier.
14. A method for the treatment of raf-mediated disease states in humans
and/or other mammals, which comprises administering a compound of formula I or a
30 salt, prodrug or isolated stereoisomer thereof to a human or other mammal in need
thereof.

15. A method for the treatment of p38-mediated disease states in humans and/or other mammals, which comprises administering a compound of formula I of claim 1 or a salt, prodrug or isolated stereoisomer thereof to a human or other mammal in need thereof.

5

16. A method for the treatment of VEGF-mediated disease states in humans and/or other mammals, which comprises administering a compound of formula I of claim 1 or a salt, prodrug or isolated stereoisomer thereof to a human or other mammal in need thereof.

10

17. A method as in claim 16 wherein the disease mediated by the VEGF-induced signal transduction pathway that is treated is characterized by abnormal angiogenesis or hyperpermeability processes.

15

18. A method as in claim 16 wherein the disease that is treated is one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis.

20

19. A method as in claim 16 wherein the disease that is treated is one or more of the following conditions in humans and/or other mammals:

25

tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis,

in combination with an infectious disease selected from the group consisting of: tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from E.

30

coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

5

20. A method for the treatment of hyper-proliferative, inflammatory and angiogenesis disorders and osteoporosis in humans and/or other mammals which comprises administering a compound of formula I of claim 1 or a salt, prodrug or isolated stereoisomer thereof to a human or other mammal in need thereof.

10

21. A method for the treatment or prevention of cancer in humans and other mammals which comprises administering a compound of formula I of claim 1 or a salt, prodrug or isolated stereoisomer thereof to a human or other mammal in need thereof.

15

22. A method as in claim 21 wherein a compound of formula I of claim 1, or a salt, prodrug or isolated stereoisomer thereof, is administered in combination with an additional anti-proliferative agent in the same formulation or in separate formulations.

20

23. A method as in claim 22 wherein the additional anti-proliferative agent is a cytotoxic agent selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycin), epirubicin, epothilone, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine, oxaliplatin, gemcitabine, gefinitib, taxotere, ara A, ara C, herceptin, BCNU, CCNU, DTIC, and actinomycin D.

25
30

24. A method as in claim 23 wherein the additional anti-proliferative agent is selected from the group consisting aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

10

25. A method as in claim 21 for treating cancers not mediated by raf kinase.

26. A method as in claim 21 wherein a compound of formula I of claim 1 or a salt, prodrug or isolated stereoisomer thereof is administered in combination with at least one cytotoxic or cytostatic chemotherapeutic agent in the same formulation or in separate formulations.

27. A method as in claim 26 wherein the cytotoxic or cytostatic chemotherapeutic agent is selected from the group consisting of DNA topoisomerase I and II inhibitors, DNA intercalators, alkylating agents, microtubule disruptors, hormone and growth factor receptor agonists or antagonists, other kinase inhibitors and anti-metabolites.

28. A method as in claim 21 wherein a compound of formula I of claim 1, or a salt, prodrug or isolated stereoisomer thereof, is administered simultaneously with a cytotoxic or cytostatic chemotherapeutic agent to a patient with a cancer, in the same formulation.

29. A kit comprising a separate dose of a compound of formula I of claim 1, or a salt, prodrug or isolated stereoisomer thereof, and a separate dose of a cytotoxic or cytostatic chemotherapeutic agent in separate containers.

30. A method for the treatment of a condition in humans and/or other mammals which comprises administering a compound of formula I of claim 1 or a salt, prodrug or isolated stereoisomer thereof to a human or other mammal with said condition, wherein said condition is selected from the group consisting of retinopathy, ischemic retinal-vein occlusion, age related macular degeneration; psoriasis, bullous disorder associated with subepidermal blister formation, erythema multiforme, dermatitis herpetiformis, rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria and coronary thrombosis from atherosclerotic plaque, aneurismal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, temporomandibular joint disease or demyelating disease of the nervous system.

31. A method for the treatment of a condition in humans and/or other mammals which comprises administering a compound of formula I of claim 1 or a salt, prodrug or isolated stereoisomer thereof to a human or other mammal with said condition, wherein said condition is selected from the group consisting of rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelation and oligodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft

reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement.

5 32. A method of treating or preventing a hyper-proliferative disorder in humans and/or other mammals comprising administering an effective amount of a compound of formula I of claim 1 to said human or mammal.

10 33. A method as in claim 32 wherein the disease treated is selected from the group consisting of tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enterotoxin A resulting from *Staphylococcus* infection, meningococcal infection, and infections from *Borrelia burgdorferi*, *Treponema pallidum*, cytomegalovirus, influenza virus, Theiler's
15 encephalomyelitis virus, and the human immunodeficiency virus (HIV).

20 34. A method of treating or preventing osteoporosis, inflammation, and angiogenesis disorders, with the exclusion of raf-mediated cancer, in a human and/or other mammal by administering an effective amount of a compound of claim 1 to said mammal.

25 35. A method of preparing compounds of claim 1 which comprises the step oxidizing the nitrogen of pyridyl ring M to form the corresponding pyridine-1-oxide.

30

30

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/04110

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/44 A61K31/47 C07D213/89 C07D215/60 C07D217/08 A61P35/00 A61P29/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 32436 A (BAYER AG) 1 July 1999 (1999-07-01) claims 15,16; tables 1-5 ---	1-35
Y	WO 00 42012 A (RIEDL BERND ;LOWINGER TIMOTHY B (JP); DUMAS JACQUES (US); RENICK J) 20 July 2000 (2000-07-20) claims 1,62; tables 3-6 -----	1-35
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *G* document member of the same patent family		
Date of the actual completion of the international search 24 June 2003		Date of mailing of the international search report 02/07/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Bérillon, L

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/04110

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14-28 and 30-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-35 relate to compounds defined by reference to a desirable characteristic or property, namely prodrugs of formula (I). The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I), salts or stereoisomers thereof.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/04110

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9932436	A	01-07-1999	AU 1905499 A	12-07-1999
			BG 104599 A	30-03-2001
			BR 9814375 A	21-05-2002
			CA 2315646 A1	01-07-1999
			CN 1283180 T	07-02-2001
			DE 1049664 T1	03-05-2001
			EP 1049664 A1	08-11-2000
			ES 2153809 T1	16-03-2001
			GR 2001300006 T1	28-02-2001
			HU 0004437 A2	28-06-2001
			JP 2001526258 T	18-12-2001
			NO 20003230 A	21-08-2000
			PL 342078 A1	21-05-2001
			SK 9612000 A3	12-03-2001
			TR 200002616 T2	21-11-2000
			TR 200100874 T2	21-06-2001
			WO 9932436 A1	01-07-1999
WO 0042012	A	20-07-2000	AU 2501600 A	01-08-2000
			BG 105763 A	29-03-2002
			CA 2359510 A1	20-07-2000
			CN 1341098 T	20-03-2002
			CZ 20012489 A3	16-01-2002
			EE 200100368 A	15-04-2003
			EP 1140840 A1	10-10-2001
			HR 20010580 A1	31-08-2002
			NO 20013463 A	12-09-2001
			SK 9882001 A3	04-04-2002
			TR 200102020 T2	21-01-2003
			WO 0042012 A1	20-07-2000
			US 2001034447 A1	25-10-2001
			US 2001027202 A1	04-10-2001
			US 2001011135 A1	02-08-2001
			US 2001016659 A1	23-08-2001
			US 2001011136 A1	02-08-2001
			US 2002165394 A1	07-11-2002
			US 2002137774 A1	26-09-2002
			US 2002042517 A1	11-04-2002